Reference Example 10

6-Methoxy-2-(N-methylamino)methyltetralin hydrochloride

An acetonitrile (400 ml) solution of N-(6-methoxy-1-oxo-2-tetralinyl)methyl-N,N,N-trimethylammonium iodide (44.5 g), N-benzyl-N-methylamine (14.4 g) and triethylamine (18 ml) was heated under reflux for 16 hours. The reaction mixture was concentrated, then water (200 ml) was added to the resulting residue, and an aqueous solution of 1 N sodium hydroxide was added to this to make it have pH of 9, which was then extracted with ethyl acetate (200 ml). The organic layer was washed with water, dried, and then concentrated. The residue was dissolved in methanol, and sodium borohydride (7.1 g) was added thereto, with cooling with ice, and then stirred at room temperature for 16 hours. The reaction mixture was concentrated, then water (200 ml) was added to the resulting residue, and an aqueous solution of 1 N sodium hydroxide was added to this to make it have pH of 9, which was then extracted with ethyl acetate (200 ml). The organic layer was washed with water, dried and then concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/1). Concentrated hydrochloric acid (26 ml) and 10% palladium-carbon (3 g) were added to an ethanol solution (200 ml) of the effective fraction obtained through the chromatography. The reaction mixture was catalytically reduced under atmospheric hydrogen pressure for 48 hours. The catalyst was removed from the mixture through filtration, and the resulting filtrate was concentrated. The crystals formed were washed with acetone to obtain the entitled compound (8.17 g).

m.p.: 192-193°C.

Reference Example 11

2-Aminomethyl-6-methoxytetralin hydrochloride

The entitled compound was obtained in the same manner as in Reference Example 10.

m.p. 217-218°C.

Solvent for recrystallization: ethanol-diisopropyl ether

Reference Example 12

N-(6-Methoxy-2-tetralinyl)methylacetamide

Acetyl chloride (0.67 g) was added to a pyridine solution (15 ml) of 2-aminomethyl-6-methoxytetralin hydrochloride (1.5 g; obtained in Reference Example 11), and the reaction mixture was stirred at room temperature for 16 hours, to which was added ethyl acetate. The organic layer was washed with 1 N hydrochloric acid and a saturated aqueous sodium bicarbonate solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-diisopropyl ether to obtain the entitled compound (960 mg).

m.p.: 96-97°C.

Reference Example 13

N,N-Dimethyl-(6-methoxy-2-tetralin)acetamide

(6-Methoxy-2-tetralin)acetic acid (1.491 g), dimethylamine hydrochloride (0.846 g), WSC (1.726 g), 1-hydroxybenzotriazole (1.069 g) and triethylamine (2.8 ml) were added to acetonitrile (30 ml). The reaction mixture was stirred at room temperature for 20 hours, and 1 N hydrochloric acid was added thereto, which was then extracted with ethyl acetate. The organic layer was separated, washed with water, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by silica gel column

chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain the entitled compound (1.667 g).

^{1}H NMR δ: 1.34-1.57(1H,m), 1.91-2.08(1H,m), 2.22-2.51(2H,m), 2.36(2H,s), 2.77-2.94(3H,m),2.98(3H,s), 3.02(3H,s), 3.77(3H,s), 6.59-6.72(2H,m), 6.96(1H,d,J=8Hz).

Reference Example 14

2-[2-(N,N-dimethylamino)ethyl]-6-methoxytetralin hydrochloride

Lithium aluminum hydride (0.25 g) was added to a THF solution (20 ml) of N,N-dimethyl-(6-methoxy-2-tetralin)acetamide (1.613 g; obtained in Reference Example 13). The reaction mixture was stirred at room temperature for 6 hours, to which was added water. Insoluble substances were removed from the reaction mixture through filtration, and the filtrate was concentrated. The residue was processed with a solution of 4 N hydrochloric acid-ethyl acetate to obtain its hydrochloride, which was then recrystallized from methanol-ethyl acetate to obtain the entitled compound (1.247 g).

m.p.: 183-185°C.

Reference Example 15

2-[N-Benzyl-N-(3,3-diphenylpropyl)amino]methyl-6-methoxytetralin

2-(N-benzylamino)methyl-6-methoxytetralin hydrochloride (0.602 g; obtained in Reference Example 6), 3,3-diphenylpropyl iodide (0.803 g) and potassium carbonate (0.800 g) were added to DMF (20 ml). The reaction mixture was stirred at room temperature for 24 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium

chloride solution, then dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain the entitled compound (0.335 g).

^{1}H NMR δ: 1.11-1.40(1H,m), 1.70-2.05(2H,m), 2.13-2.48(7H,m), 2.62-2.88(3H,m), 3.54(2H,s), 3.76(3H,s), 3.98(1H,t,J=8Hz), 6.55-6.70(2H,m), 6.95(1H,d,J=8Hz), 7.04-7.38(15H,m).

Reference Example 16

2-(N,N-Dimethylamino)methyl-6-hydroxytetralin hydrochloride

2-(N,N-Dimethylamino)methyl-6-methoxytetralin hydrochloride (0.365 g; obtained in Reference Example 5) was added to 48% hydrobromic acid (10 ml), and the reaction mixture was heated under reflux for 3 hours, and then left cooled. This was neutralized with an aqueous solution of 1 N sodium hydroxide, and a solution of 10% potassium carbonate was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/2), and then processed with a solution of 4 N hydrochloric acid-ethyl acetate to obtain its hydrochloride. This was washed with ethyl acetate to obtain the entitled compound (0.211 g).

m.p.: 221-224°C.

Compounds of the following Reference Examples 17 to 22 were obtained in the same manner as in Reference Example 16.

Reference Example 17

2-(N,N-Dipropylamino)methyl-6-hydroxytetralin

hydrochloride

m.p.: 173-175° C.

Solvent for recrystallization: methanol-diisopropyl ether

Reference Example 18

2-[N-Benzyl-N-(3,3-diphenylpropyl)amino]methyl-6-hydroxytetralin

^{1}H NMR δ: 1.10-1.34(1H,m), 1.68-2.02(2H,m), 2.12-2.48(7H,m), 2.57-2.87(3H,m), 3.55(2H,d,J=2Hz), 3.98(1H,t,J=8Hz), 6.48-6.60(2H,m), 6.89(1H,d,J=8Hz), 7.04-7.34(15H,m).

Reference Example 19

6-Hydroxy-2-piperidinomethyltetralin hydrochloride

m.p.: 216-218° C.

Solvent for recrystallization: methanol-diethyl ether

Reference Example 20

2-[2-(N,N-Dimethylamino)ethyl]-6-hydroxytetralin

m.p.: 114-116° C.

Solvent for recrystallization: ethyl acetate-hexane

Reference Example 21

2-(N,N-Dimethylamino)methyl-7-hydroxytetralin hydrochloride

m.p.: 197-198° C.

Solvent for recrystallization: methanol-ethyl acetate

Reference Example 22

6-Hydroxy-2-(N-methylamino)methyltetralin hydrochloride

m.p.: 229-230° C.

Solvent for recrystallization: methanol-ethyl acetate

Reference Example 23

N-[6-(4-Biphenylyl)methoxy-2-tetralinyl]methylacetamide

Boron tribromide (1.57 g) was added to a methylene chloride (15 ml) solution of N-(6-methoxy-2-tetralinyl)methylacetamide (730 mg; obtained in Reference Example 12), at 0°C. The reaction mixture was warmed to room temperature, and stirred for 1 hour. Water was added to this, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous potassium carbonate solution, then dried, and concentrated. The residue was dissolved in DMF (20 ml), to which were added 4-(iodomethyl)biphenyl (1.35 g) and potassium carbonate (1.36 g). The reaction mixture was stirred at room temperature for 16 hours. Water was added to this, which was then extracted with ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1). The resulting crude crystals were recrystallized from ethyl acetate-diisopropyl ether to obtain the entitled compound (750 mg).

m.p.: 144-145°C.

Reference Example 24

Methyl (6-hydroxy-2-tetralin)acetate

(6-Methoxy-2-tetralin)acetic acid (15.22 g) was added to 48% hydrobromic acid (100 ml), and the reaction mixture was heated under reflux for 3 hours. After this was cooled, water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting residue was dissolved in methanol (200

ml), to which was dropwise added thionyl chloride (6.0 ml) at 0° C. The reaction mixture was stirred at room temperature for 2 hours, and then concentrated. Water was added to the residue, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the entitled compound (9.566 g).

^{1}H NMR δ: 1.32-1.55(1H,m), 1.84-2.00(1H,m), 2.10-2.48(4H,m), 2.70-2.89(3H,m), 3.71(3H,s), 4.80(1H,s), 6.52-6.64(2H,m), 6.91(1H,d,J=8Hz).

Reference Example 25

Methyl [6-(2-naphthyl)methoxy-2-tetralin]acetate

Methyl (6-hydroxy-2-tetralin)acetate (0.608 g; obtained in Reference Example 24), 2-naphthylmethyl bromide (0.737 g) and potassium carbonate (0.59 g) were added to DMF (20 ml). The reaction mixture was stirred at room temperature for 5 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4), and then recrystallized from ethyl acetate-hexane to obtain the entitled compound (0.624 g).

m.p.: 73-75° C.

Reference Example 26

2-(2-Hydroxyethyl)-6-(2-naphthyl)methoxytetralin

Lithium aluminum hydride (75 mg) was added to a THF solution (10 ml) of methyl [6-(2-naphthyl)methoxy-2-tetralin]acetate (0.712 g; obtained in Reference Example 25). The reaction mixture was stirred at room

temperature for 2 hours, and then water was added thereto. Insoluble substances were removed from the reaction mixture through filtration, and the filtrate was concentrated. The resulting crystals were recrystallized from ethyl acetate-hexane to obtain the entitled compound (0.451 g).

m.p.: 90-91°C.

Reference Example 27

2-(2-Iodoethyl)-6-(2-naphthyl)methoxytetralin

P-Toluenesulfonyl chloride (0.301 g) was added to a dichloromethane solution (15 ml) of 2-(2-hydroxyethyl)-6-(2-naphthyl)methoxytetralin (0.712 g; obtained in Reference Example 26) and pyridine (0.19 ml), at 0°C. The reaction mixture was stirred at room temperature for 24 hours, and 1 N hydrochloric acid was added thereto, which was then extracted with dichloromethane. The organic layer was washed with water, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was dissolved in acetone (10 ml), to which was added sodium iodide (0.371 g). The reaction mixture was heated under reflux for 4 hours, and then concentrated. A saturated aqueous sodium bicarbonate solution and an aqueous sodium thiosulfate solution were added to this, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/10) to obtain the entitled compound (0.451 g).

^{1}H NMR δ: 1.30-1.60(1H,m), 1.75-2.02(4H,m), 2.26-2.46(1H,m), 2.72-2.89(3H,m), 3.30(2H,t,J=7Hz), 5.19(2H,s), 6.72-6.83(2H,m), 6.98(1H,d,J=8Hz), 7.42-

7.57(3H,m), 7.78-7.91(4H,m).

Reference Example 28

Methyl [6-(4-biphenylyl)methoxy-2-tetralin]acetate

60% oily sodium hydride (1.034 g) was added to a DMF solution (100 ml) of methyl (6-hydroxy-2-tetralin)acetate (4.407 g; obtained in Reference Example 24), at 0°C. The reaction mixture was stirred at 40°C for 1 hour, and then again cooled to 0°C, to which was then added 4-(chloromethyl)biphenyl (4.466 g). The reaction mixture was stirred at room temperature for 14 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were washed with diisopropyl ether to obtain the entitled compound (3.995 g).

m.p.: 65-70°C.

Reference Example 29

[6-(4-Biphenylyl)methoxy-2-tetralin]acetic acid

Methyl [6-(4-biphenylyl)methoxy-2-tetralin]acetate (3.480 g; obtained in Reference Example 28) was dissolved in THF (80 ml) and methanol (40 ml), to which was added an aqueous solution of 1 N sodium hydroxide (20 ml). The reaction mixture was stirred at room temperature for 7 hours, and then concentrated. 1 N hydrochloric acid was added to the residue until the resulting mixture became acidic, and this was then extracted with a mixed solvent of ethyl acetate and THF. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from THF-diisopropyl ether to obtain the entitled compound (2.956 g).

m.p.: 167-169°C.

Reference Example 30

6-[(4-Biphenylyl)methoxy-2-tetralin]-N,N-dimethylacetamide

[6-(4-Biphenylyl)methoxy-2-tetralin]acetic acid (1.866 g; obtained in Reference Example 29), dimethylamine hydrochloride (0.553 g), WSC (1.512 g), 1-hydroxybenzotriazole (0.764 g) and triethylamine (2.1 ml) were added to a mixture of acetonitrile (50 ml) and THF (50 ml). The reaction mixture was stirred at room temperature for 20 hours, and 1 N hydrochloric acid was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the entitled compound (1.497 g).

m.p.: 114-119°C.

Reference Example 31

6-Acetylamino-2-(N,N-dimethylamino)methyltetralin

A THF solution (40 ml) of 6-acetylamino-1-tetralone (1.692 g) was added to an acetonitrile solution (40 ml) of N,N-dimethylmethylene ammonium chloride (2.04 g), then stirred at room temperature for 24 hours, and concentrated. An aqueous solution of 10% potassium carbonate was added to the residue, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was dissolved in methanol (50 ml), to which was added sodium borohydride (0.86 g). The reaction mixture was stirred at room temperature for 1 hour, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with a saturated

aqueous sodium chloride solution, then dried, and concentrated. The residue was dissolved in methanol (50 ml), to which were added 10% palladium-carbon (0.4 g) and 1 N hydrochloric acid (20 ml). Then, this was catalytically reduced under a hydrogen pressure of 1 atmosphere, for 12 hours. The palladium-carbon was removed from the reaction mixture through filtration, the filtrate was concentrated, and an aqueous solution of 10% potassium carbonate was added thereto to form a free form compound. Then, this was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the entitled compound (1.862 g).

m.p.: 104-107°C.

Reference Example 32

6-Amino-2-(N,N-dimethylamino)methyltetralin

6-Acetylamino-2-(N,N-dimethylamino)methyltetralin hydrochloride (0.879 g; obtained in Reference Example 31) was added to 2 N hydrochloric acid. The reaction mixture was heated under reflux for 90 minutes, and then an aqueous solution of 1 N sodium hydroxide was added thereto to thereby make the resulting mixture have pH of 9. Then, this was extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain the entitled compound (0.231 g).

^{1}H NMR δ: 1.24-1.47(1H,m), 1.60-2.00(3H,m), 2.13-2.40(2H,m), 2.24(6H,s), 2.66-2.89(3H,m), 3.23-2.73(2H,br), 6.42-6.52(2H,m), 6.89(1H,d,J=8Hz).

Reference Example 33

6-(4-Bromobenzyl)oxy-2-(N,N-dimethylamino)methyltetralin

2-(N,N-Dimethylamino)methyl-6-hydroxytetralin (5.0 g; obtained in Reference Example 16) was dissolved in DMF (130 ml), to which was added 60% oily sodium hydride (1.46 g) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 1 hour. This was again cooled to 0°C, to which was added a DMF solution (20 ml) of 4-bromobenzyl bromide (10.0 g). The reaction mixture was stirred at room temperature for 2 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/10) to obtain the entitled compound (3.4 g).

^{1}H NMR δ: 1.2-1.5(1H,m), 1.7-2.1(2H,m), 2.1-2.5(3H,m), 2.24(6H,s), 2.7-3.0(3H,m), 4.97(2H,s), 6.6-6.8(2H,m), 7.00(1H,d,J=8Hz), 7.28(2H,d,J=8Hz), 7.50(2H,d,J=8Hz).

Compounds of the following Reference Examples 34 to 40 were obtained in the same manner as in Reference Example 33.

Reference Example 34

6-(3-Bromobenzyl)oxy-2-(N,N-dimethylamino)methyltetralin

^{1}H NMR δ: 1.2-1.5(1H,m), 1.7-2.1(2H,m), 2.1-2.5(3H,m), 2.24(6H,s), 2.7-3.0(3H,m), 4.99(2H,s), 6.6-6.8(2H,m), 7.01(1H,d,J=8Hz), 7.1-7.5(3H,m), 7.59(1H,s).

Reference Example 35

6-(2-Bromobenzyl)oxy-2-(N,N-dimethylamino)methyltetralin

^{1}H NMR δ: 1.2-1.5(1H,m), 1.7-2.1(2H,m), 2.1-2.5(3H,m), 2.24(6H,s), 2.7-3.0(3H,m), 5.09(2H,s), 6.7-6.8(2H,m), 7.02(1H,d,J=8Hz), 7.17(1H,td,J=7Hz,2Hz), 7.32(1H,td,J=7Hz,2Hz), 7.5-7.6(2H,m).

Reference Example 36

6-Benzyloxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

m.p.: 196-198°C.

Solvent for recrystallization: methanol-ethyl acetate

Reference Example 37

6-(2-Chlorobenzyl)oxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

m.p.: 203-207°C.

Solvent for recrystallization: methanol-diethyl ether

Reference Example 38

6-(2,4-Dichlorobenzyl)oxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

m.p.: 217-218°C.

Solvent for recrystallization: methylene chloride-diethyl ether

Reference Example 39

6-(4-Benzyloxybenzyl)oxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

m.p.: 208-209°C.

Solvent for recrystallization: ethanol-ethyl acetate

Reference Example 40

2-[N-Benzyl-N-(3,3-diphenylpropyl)amino]methyl-6-(2,4-dichlorobenzyl)oxytetralin hydrochloride

This was amorphous powder.

^{1}H NMR δ: 1.12-1.35(1H,m), 1.72-2.06(2H,m), 2.14-2.48(7H,m), 2.54-2.88(3H,m), 3.55(2H,d,J=2Hz), 3.98(1H,t,J=7Hz), 5.07(2H,s), 6.63-6.74(2H,m),

6.96(1H,d,J=8Hz), 7.06-7.34(15H,m), 7.37-7.53(3H,m).

IR (KBr): 3058, 3028, 2925, 2572, 1592, 1500, 1234, 747, 701 cm^{-1}.

Reference Example 41

Methyl [6-(4-bromobenzyl)oxy-2-tetralin]acetate

Methyl (6-hydroxy-2-tetralin)acetate (17.5 g), 4-bromobenzyl bromide (24.0 g) and potassium carbonate (30.6 g) were added to DMF (160 ml). The reaction mixture was stirred at room temperature for 12 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from toluene-diisopropyl ether to obtain the entitled compound (31.0 g).

m.p.: 78-79°C.

Reference Example 42

[6-(4-Bromobenzyl)oxy-2-tetralin]acetic acid

Methyl [6-(4-bromobenzyl)oxy-2-tetralin]acetate (31.0 g) was dissolved in methanol (200 ml), to which was added an aqueous solution of 1 N sodium hydroxide (200 ml). The reaction mixture was stirred at 80°C for 4 hours, and then concentrated. 1 N hydrochloric acid was added to the residue until the resulting mixture became acidic, and this was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the entitled compound (29.4 g).

m.p.: 145-146°C.

Reference Example 43

Methyl 3-(6-methoxy-2-methoxycarbonyl-1-oxo-2-tetralin)propionate

A 28% sodium methoxide-methanol solution (17.3 g) was added to a methanol solution (100 ml) of methyl (6-

methoxy-1-oxo-2-tetralin)carboxylate (21 g; described in J. Am. Chem. Soc., Vol. 78, p. 461, 1951). To the reaction mixture was added a methanol solution (100 ml) of methyl acrylate (9.7 ml), and stirred at room temperature for 3 hours. The reaction mixture was poured into an aqueous solution of 10% citric acid, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-diisopropyl ether to obtain the entitled compound (19.7 g).

m.p.: 66-67°C.

Reference Example 44

3-(6-Methoxy-1-oxo-2-tetralin)propionic acid

6 N Hydrochloric acid (150 ml) was added to an acetic acid solution (30 ml) of methyl 3-(6-methoxy-2-methoxycarbonyl-1-oxo-2-tetralin)propionate (17.7g), and heated under reflux for 2 hours. Water (200 ml) was added to the reaction mixture, and the crystals formed were taken out through filtration to obtain the entitled compound (13.3 g).

m.p.: 129-130°C.

Reference Example 45

4-(6-Methoxy-1-oxo-2-tetralin)butyric acid

Methyl 3-(6-methoxy-1-oxo-2-tetralin)carboxylate (20 g), ethyl 4-bromocrotonate (26.4 g) and potassium carbonate (23.6 g) were added to DMF (300 ml). The reaction mixture was stirred at 80°C for 12 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. 10% palladium-carbon (3.0 g) was added to an ethanol solution (200 ml) of the

residue, which was thus catalytically reduced under a hydrogen pressure of one atmosphere at room temperature for 12 hours. The catalyst was removed from the reaction mixture through filtration, and the filtrate was concentrated. 6 N hydrochloric acid (100 ml) was added to an acetic acid solution (50 ml) of the residue, and heated under reflux for 4 hours. Water (200 ml) was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-diisopropyl ether to obtain the entitled compound (14.0 g).

m.p.: 91-92°C.

Reference Example 46

3-(6-Methoxy-2-tetralin)propionic acid

Perchloric acid (0.25 ml) and 10% palladium-carbon (1.0 g) were added to an acetic acid solution (50 ml) of 3-(6-methoxy-1-oxo-2-tetralin)propionic acid (10 g), which was thus catalytically reduced under a hydrogen pressure of one atmosphere at room temperature for 24 hours. The catalyst was removed from the reaction mixture through filtration, and the filtrate was concentrated. Water was added to the residue, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from toluene-diisopropyl ether to obtain the entitled compound (6.6 g).

m.p.: 114-115°C.

Reference Example 47

4-(6-Methoxy-2-tetralin)butyric acid

The entitled compound was obtained in the same manner as in Reference Example 46.

m.p.: 100-101°C.

Solvent for recrystallization: toluene-diisopropyl ether

Reference Example 48

[6-(4-Bromobenzyl)oxy-2-tetralin]-N,N-dimethylacetamide

[6-(4-Bromobenzyl)oxy-2-tetralin]acetic acid (15.0 g), dimethylamine hydrochloride (4.24 g), WSC (12.0 g), 1-hydroxybenzotriazole (6.13 g) and triethylamine (16.7 ml) were added to a mixed solvent of acetonitrile (200 ml) and THF (200 ml). The reaction mixture was stirred at room temperature for 12 hours, and 1 N hydrochloric acid was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, then dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the entitled compound (14.3 g).

m.p.: 86-87°C.

Compounds of the following Reference Examples 49 and 50 were obtained in the same manner as in Reference Example 48.

Reference Example 49

N,N-Dimethyl-3-(6-methoxy-2-tetralin)propionamide

This was oily.

^{1}H NMR δ: 1.32-1.54(1H,m), 1.60-1.84(3H,m), 1.84-2.02(1H,m),2.26-2.50(3H,m), 2.70-2.90(3H,m), 2.95(3H,s),3.03(3H,s), 3.76(3H,s), 6.56-6.72(2H,m), 6.97(1H,d,J=8Hz).

Reference Example 50

N,N-Dimethyl-4-(6-methoxy-2-tetralin)butanamide

This was oily.

^{1}H NMR δ: 1.30-1.50(3H,m), 1.60-1.84(3H,m), 1.84-2.00(1H,m), 2.24-2.44(3H,m), 2.70-2.90(3H,m), 2.95(3H,s), 3.01(3H,s), 3.76(3H,s), 6.56-6.72(2H,m), 6.97(1H,d,J=8Hz).

Reference Example 51

6-(4-Bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride

Lithium aluminum hydride (1.95 g) was added to a THF solution (300 ml) of [6-(4-bromobenzyl)oxy-2-tetralin]-N,N-dimethylacetamide (13.8 g). The reaction mixture was stirred at room temperature for 2 hours, and then an aqueous solution of 1 N sodium hydroxide was added thereto. Insoluble substances were removed from the reaction mixture through filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate to methanol), and then processed with a solution of 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-ethyl acetate to obtain the entitled compound (10.5 g).

m.p.: 200-202°C.

Compounds of the following Reference Examples 52 and 53 were obtained in the same manner as in Reference Example 51.

Reference Example 52

2-[3-(N,N-Dimethylamino)propyl]-6-methoxytetralin hydrochloride

m.p.: 163-164°C.

Solvent for recrystallization: methanol-diisopropyl ether

Reference Example 53

2-[4-(N,N-Dimethylamino)butyl]-6-methoxytetralin hydrochloride

m.p.: 144-145°C.

Solvent for recrystallization: methanol-diisopropyl ether

Reference Example 54

2-[3-(N,N-Dimethylamino)propyl]-6-hydroxytetralin hydrochloride

2-[3-(N,N-Dimethylamino)propyl]-6-methoxytetralin hydrochloride (3.6 g) was added to 48% hydrobromic acid (20 ml), and the reaction mixture was heated under reflux for 3 hours, and then left cooled. This was neutralized with an aqueous solution of 1 N sodium hydroxide, and an aqueous solution of 10% potassium carbonate was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (2.0 g).

m.p.: 110-111°C.

Reference Example 55

2-[4-(N,N-Dimethylamino)butyl]-6-hydroxytetralin hydrochloride

The entitled compound was obtained in the same manner as in Reference Example 54.

m.p.: 123-124°C.

Solvent for recrystallization: methanol-diisopropyl ether

Reference Example 56

N,N-Dimethyl-(6-methoxy-1-oxo-2-tetralin)acetamide

Dimethylamine hydrochloride (24.3 g, 298 mmols), WSC (66.0 g, 344 mmols) and 1-hydroxybenzotriazole

hydrate (35.1 g, 230 mmols) were added to an acetonitrile solution (1 liter) of (6-methoxy-1-oxo-2-tetralin)acetic acid (53.8 g, 230 mmols; described in Eur. J. Med. Chem., Vol. 25, p. 765, 1990). Triethylamine (96 ml, 689 mmols) was added to the reaction mixture with cooling with ice, and stirred at room temperature for 48 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-toluene to obtain the entitled compound (34 g).

m.p.: 102-104°C.

Reference Example 57

N,N-Dimethyl[6-methoxy-2-(3,4-dihydronaphthalene)]acetamide

Sodium borohydride (15 g, 397 mmols) was divided into 3 portions, which were separately added to a methanol solution (1 liter) of N,N-dimethyl-(6-methoxy-1-oxo-2-tetralin)acetamide (44.7 g, 180 mmols) with cooling with ice. The reaction mixture was stirred at room temperature for 2 hours, then neutralized with 1 N hydrochloric acid, and concentrated under reduced pressure to about 1/3. Water was added to the concentrate, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated under reduced pressure. P-toluenesulfonic acid hydrate (700 mg, 4.06 mmols) was added to a toluene solution (700 ml) of the resulting residue, and heated under reflux for 30 minutes. The reaction mixture was washed with a saturated aqueous sodium bicarbonate solution and a saturated aqueous

sodium chloride solution, then dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/1 to ethyl acetate alone) to obtain the entitled compound (37.5 g).

^{1}H NMR δ: 2.30(2H,t,J=8.0Hz), 2.83(2H,t,J=8.0Hz), 2.99(3H,s), 3.04(3H,s), 3.26(2H,s), 3.79(3H,s), 6.21(1H,s), 6.62-6.72(2H,m), 6.86-6.96(1H,m).

Reference Example 58

(-)-N,N-Dimethyl-(6-methoxy-2-tetralin)acetamide

Degassed ethanol (160 ml) was added to N,N-dimethyl-[6-methoxy-2-(3,4-dihydronaphthalene)]acetamide (18.03 g, 73.50 mmols) and $[RuCl_2[(R)-(BINAP)]]_2NEt_3$ (1.24 g, 0.734 mmols), and the resulting solution was transferred into an autoclave, in which the solution was stirred under a hydrogen pressure of 100 kg/cm^2, at 70°C for 6 hours. This was concentrated to dryness under reduced pressure, and the residue was subjected to silica gel column chromatography (eluent: hexane/ethyl acetate = 1/2) to obtain the entitled compound (15.5 g, 98.3% e.e.).

m.p.: 70-71°C.

Solvent for recrystallization: ethyl acetate-hexane

$[\alpha]_D^{25}$ = -61.3° (c = 1.00, chloroform)

Elemental Analysis: for $C_{15}H_{21}NO_2$

Calc.:	C 72.84,	H 8.56,	N 5.66
Found:	C 72.76,	H 8.49,	N 5.79

Reference Example 59

(+)-N,N-Dimethyl-(6-methoxy-2-tetralin)acetamide

Degassed ethanol (160 ml) was added to N,N-dimethyl-[6-methoxy-2-(3,4-dihydronaphthalene)]acetamide (18.06 g, 73.50 mmols)

and $[RuCl_2[(S)-(BINAP)]]_2NEt_3$ (1.24 g, 0.734 mmols), and the resulting solution was transferred into an autoclave, in which the solution was stirred under a hydrogen pressure of 100 kg/cm^2, at 70°C for 6 hours. This was concentrated to dryness under reduced pressure, and the residue was subjected to silica gel column chromatography (eluent: hexane/ethyl acetate = 1/2) to obtain the entitled compound (15.8 g, 98.7% e.e.).

m.p.: 71-72°C.

Solvent for recrystallization: ethyl acetate-hexane

$[\alpha]_D^{25}$ = +63.7° (c = 1.00, chloroform)

Elemental Analysis: for $C_{15}H_{21}NO_2$

Calc.:	C 72.84,	H 8.56,	N 5.66
Found:	C 72.68,	H 8.42,	N 5.65

Reference Example 60

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-methoxytetralin hydrochloride

Lithium aluminum hydride (0.203 g) was added to a THF solution (15 ml) of (+)-N,N-dimethyl-(6-methoxy-2-tetralin)acetamide (0.870 g). The reaction mixture was stirred at room temperature for 50 minutes, then heated under reflux for 30 minutes, and thereafter left cooled. Water was added to this, from which were removed insoluble substances through filtration, and the filtrate was then concentrated. The residue was purified by alumina column chromatography (eluent: hexane alone to ethyl acetate/hexane = 1/10 to 1/4), and then processed with a solution of 4 N hydrochloric acid-ethyl acetate solution to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.749 g).

m.p.: 195-197°C.

$[\alpha]_D^{20}$ = +68.2° (c = 0.55, methanol)

Reference Example 61

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-hydroxytetralin hydrochloride

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-methoxytetralin hydrochloride (0.602 g) was added to 48% hydrobromic acid (10 ml), and the reaction mixture was heated under reflux for 3.5 hours, and then left cooled. This was neutralized with an aqueous solution of 1 N sodium hydroxide, and a solution of 10% potassium carbonate was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was processed with a solution of 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.490 g).

m.p.: 213-215° C.

$[\alpha]_D^{20}$ = +69.1° (c = 0.52, methanol)

Reference Example 62

(-)-2-[2-(N,N-dimethylamino)ethyl]-6-methoxytetralin hydrochloride

Lithium aluminum hydride (0.130 g) was added to a THF solution (15 ml) of (-)-N,N-dimethyl-(6-methoxy-2-tetralin)acetamide (0.807 g). The reaction mixture was stirred at room temperature for 15 minutes, then heated under reflux for 15 minutes, and thereafter left cooled. Water was added to this, from which were removed insoluble substances, and the filtrate was concentrated. The residue was purified by alumina column chromatography (eluent: hexane alone to ethyl acetate/hexane = 1/4), and then processed with a

solution of 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.683 g).

m.p.: 193-195°C.

$[\alpha]_D^{20}$ = -68.0° (c = 0.49, methanol)

Reference Example 63

(-)-2-[2-(N,N-Dimethylamino)ethyl]-6-hydroxytetralin hydrochloride

(-)-2-[2-(N,N-Dimethylamino)ethyl]-6-methoxytetralin hydrochloride (0.563 g) was added to 48% hydrobromic acid (10 ml), and the reaction mixture was heated under reflux for 4 hours, and then left cooled. This was neutralized with an aqueous solution of 1 N sodium hydroxide, and a solution of 10% potassium carbonate was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was processed with a solution of 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.480 g).

m.p.: 213-215°C.

$[\alpha]_D^{20}$ = -69.9° (c = 0.55, methanol)

Reference Example 64

6-(4-Biphenylyl)methoxy-2-(2-hydroxyethyl)tetralin

To a suspension of lithium aluminum hydride (4.71 g) in THF (200 ml) was added a solution of methyl 6-(4-biphenylyl)methoxy-2-tetralinacetate (24.0 g) in THF (50 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 2 hr and diluted with saturated aqueous Rochelle salt. The precipitate was

filtered off and the filtrate was concentrated. The residue was recrystallized from ethyl acetate-hexane to obtain the titled compound (22.1 g).

m.p.: 101-102°C.

Reference Example 65

6-(4-Biphenylyl)methoxy-2-(2-iodoethyl)tetralin

To a solution of triphenylphosphine (12.5 g) in THF (200 ml) were successively added imidazole (3.25 g) and iodine (12.1 g). A solution of 6-(4-biphenylyl)methoxy-2-(2-hydroxyethyl)tetralin (13.15 g) in THF (100 ml) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 5 min, diluted with water, and extracted with ethyl acetate. The organic layer was washed with aqueous sodium thiosulfate and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent; toluene) to obtain the titled compound (13.2 g).

^{1}H NMR δ: 1.30-1.60 (1H, m), 1.75-2.00 (4H, m), 2.20-2.46 (1H, m), 2.72-2.92 (3H, m), 3.30 (2H, t, J=7Hz), 5.07 (2H, s), 6.70-6.84 (2H, m), 6.99 (1H, d, J=8Hz), 7.14-7.66 (9H, m).

Reference Example 66

(+)-6-(4-Bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride

To a suspension of (+)-2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (9.2 g) in toluene (180 ml) was added sodium hydride (60% in oil, 2.0 g). After stirring at 50°C for 30 min, a solution of 4-bromobenzyl chloride (9.7 g) in toluene (45 ml) was added to the reaction mixture, which was heated under reflux for one hr. The reaction mixture was

diluted with water and concentrated. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was dissolved in solvent mixture of ethyl acetate/hexane (1 : 4) and the precipitate was filtered off. The filtrate was concentrated and the residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 50 to 1 : 4) and converted into its hydrochloride. The crystals were washed with diisopropyl ether to obtain the titled compound (17.0 g).

m.p.: 191-193°C.

$[\alpha]_D^{20}$=+44.1° (c=0.99 in methanol).

Reference Example 67

N,N-Diethyl-(6-methoxy-1-oxo-2-tetralin)acetamide

To a solution of (6-methoxy-1-oxo-2-tetralin)acetic acid (30 g) in acetonitrile (500 ml) were added diethylamine (18.7 g), WSC (36.8 g), and 1-hydroxybenzotriazole (19.6 g). The reaction mixture was stirred at room temperature for 2 days and concentrated. The residue was diluted with ethyl acetate and washed with 0.5 N aqueous hydrochloric acid, and saturated aqueous sodium bicarbonate. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate =1 : 1) and further recrystallized from ethyl acetate-diisopropyl ether to obtain the titled compound (26.8 g).

m.p.: 88-89°C.

Reference Example 68

N,N-Diethyl-[6-methoxy-2-(3,4-dihydronaphthalene)]acetamide

To a solution of N,N-diethyl-(6-methoxy-1-oxo-2-tetralin)acetamide (25 g) in methanol (400 ml) was added sodium borohydride (6.54 g) in an ice bath. After stirring at room temperature for 30 min, the reaction mixture was neutralized by adding 1 N aqueous hydrochloric acid. The reaction mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried, and concentrated. The residue was dissolved in degassed toluene (300 ml) followed by addition of p-toluenesulfonic acid monohydrate (20 mg). The reaction mixture was heated under reflux for 1 hr and cooled to room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, dried and concentrated. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate =1 : 1) to obtain the titled compound (23.1 g).

^{1}H NMR δ: 1.10-1.25 (6H, m), 2.31 (2H, t, J=7.6 Hz), 2.82 (2H, t, J=7.6 Hz), 3.23 (2H, s), 3.26-3.48 (4H, m), 3.78(3H, s), 6.22 (1H, s), 6.62-6.72 (2H, m), 6.84-6.96 (1H, m).

Reference Example 69

(+)-N,N-Diethyl-(6-methoxy-2-tetralin)acetamide

N,N-Diethyl-[6-methoxy-2-(3,4-dihydronaphthalene)]acetamide (10.0 g) and $Ru_2Cl_4[(S)\text{-}BINAP]_2NEt_3$ (618 mg) were added to degassed ethanol (170 ml). The reaction mixture was stirred under hydrogen (100 kg/cm^2) at 70° C for 6 hr in an autoclave. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=2 : 1) and alumina column chromatography (eluent; hexane : ethyl acetate=4 : 1)

to obtain the titled compound (8.8 g).

$[\alpha]_D^{20}$=+54.0° (c= 1.000 in methanol).

^{1}H NMR δ: 1.00-1.22 (6H, m), 1.30-1.56 (1H, m), 1.88-2.08 (1H, m), 2.20-2.50 (4H, m), 2.70-3.00 (3H, m), 3.26-3.46 (4H, m), 3.77 (3H, s), 6.60-6.75 (2H, m), 6.96 (1H, d, J=8.0Hz).

Optical purity: 94% e.e. (by HPLC analysis).

Reference Example 70

(-)-N,N-Diethyl-(6-methoxy-2-tetralin)acetamide

N,N-Diethyl-[6-methoxy-2-(3,4-dihydronaphthalene)]acetamide (10.0 g) and Ru_2Cl_4[(R)-BINAP]$_2$NEt$_3$ (618 mg) were added to degassed ethanol(170 ml). The reaction mixture was stirred under hydrogen (100 kg/cm^2) at 70° C for 6 hr in an autoclave. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=2 : 1) and further purified by alumina column chromatography (eluent; hexane: ethyl acetate=4 : 1) to obtain the titled compound (8.88 g).

$[\alpha]_D^{20}$=-53.0° (c= 0.799 in methanol).

^{1}H NMR δ: 1.00-1.22 (6H, m), 1.30-1.56 (1H, m), 1.88-2.08 (1H, m), 2.20-2.50 (4H, m), 2.70-3.00 (3H, m), 3.26-3.46 (4H, m), 3.77 (3H, s), 6.60-6.75 (2H, m), 6.96 (1H, d, J=8.0Hz).

Optical purity: 93.7% e.e. (by HPLC analysis).

Reference Example 71

(+)-2-[2-(N,N-Diethylamino)ethyl]-6-methoxy-2-tetralin hydrochloride

To a solution of (+)-N,N-diethyl-(6-methoxy-2-tetralin)acetamide (8.8 g) in THF (150 ml) was added lithium aluminum hydride (1.45 g). The reaction mixture was stirred at room temperature and diluted with 1 N aqueous sodium hydroxide. The precipitate was

removed by filtration and the filtrate was concentrated. The residue was purified by alumina column chromatography (eluent; hexane : ethyl acetate =10 : 1) and converted into its hydrochloride, which was recrystallized from methanol-diisopropyl ether to obtain the titled compound (5.4 g).

m.p.: 144-145°C.

$[\alpha]_D^{20}$=+61.5° (c= 1.000 in methanol)

Reference Example 72

(-)-2-[2-(N,N-Diethylamino)ethyl]-6-methoxytetralin hydrochloride

The titled compound was obtained by the similar procedure as in Reference Example 71.

m.p.: 144-145°C (recrystallizing solvent: methanol-diisopropyl ether).

$[\alpha]_D^{20}$=-60.8° (c= 0.055 in methanol).

Reference Example 73

(+)-2-[2-(N,N-Diethylamino)ethyl]-6-hydroxytetralin

(+)-2-[2-(N,N-Diethylamino)ethyl]-6-methoxytetralin hydrochloride (5.2 g) was added to 48% hydrobromic acid (10 ml) and the reaction mixture was heated under reflux for 4 hr and cooled. The reaction mixture was neutralized with 1 N aqueous sodium hydroxide followed by addition of 10% aqueous potassium carbonate and extracted with the combined solvent of ethyl acetate and THF (1 : 1). The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was recrystallized from methanol-diisopropyl ether to obtain the titled compound (4.5 g).

m.p.: 102-104°C

$[\alpha]_D^{20}$=+73.8° (c= 0.226 in methanol).

Reference Example 74

(-)-2-[2-(N,N-Diethylamino)ethyl]-6-hydroxytetralin

The titled compound was synthesized from Reference Example 72, using similar method as in Reference Example 73.

m.p.: 103-104°C (recrystallizing solvent; methanol-diisopropyl ether).

$[\alpha]_D^{20}$= -73.4° (c= 1.001 in methanol).

Reference Example 75

[6-(4-Biphenylyl)methoxy-2-tetralin]-N-[2-(N,N-dimethylamino)ethyl]-N-methylacetamide hydrochloride

To a solution of [6-(4-biphenylyl)methoxy-2-tetralin]acetic acid (999 mg, Reference Example 29) in THF (15 ml) was added oxalyl chloride (0.28 ml) at 0°C. Two drops of DMF was added and the reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated and the residue was dissolved in acetonitrile (30 ml) and THF (10 ml) and a solution of N,N,N'-trimethylethylenediamine (309mg) and triethylamine (0.56 ml) in acetonitrile (5 ml) were added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for one hr, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 2) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (1.159 g).

m.p.: 190-194°C.

Reference Example 76

[6-(4-Biphenylyl)methoxy-2-tetralin]-N-[2-(N,N-diethylamino)ethyl]-N-methylacetamide hydrochloride

To a solution of [6-(4-biphenylyl)methoxy-2-tetralin]acetic acid (501 mg, Reference Example 29) in THF (15 ml) was added oxalyl chloride (0.13 ml) at 0°C. Two drops of DMF was added and the reaction mixture was stirred at room temperature for 40 min. The reaction mixture was concentrated and the residue was dissolved in acetonitrile (20 ml) and a solution of N,N-diethyl-N'-methylethylenediamine (216 mg) and triethylamine (0.28 ml) in acetonitrile (10 ml) was added at 0°C. The reaction mixture was stirred at room temperature for 45 min, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate: hexane =1 : 2) and converted into its hydrochloride, which was then recrystallized from ethanol-diisopropyl ether to obtain the titled compound (603 mg).

m.p.: 148-151°C.

Reference Example 77

[6-(4-Biphenylyl)methoxy-2-tetralin]-N-methylacetamide

A mixture of [6-(4-biphenylyl)methoxy-2-tetralin]acetic acid (1.180 g, Reference Example 29), methylamine hydrochloride (0.496 g), 1-hydroxybenzotriazole (0.509 g), WSC (0.719 g), and triethylamine (1.4 ml) in THF (30 ml) and acetonitrile (30 ml) was stirred at room temperature for 10 days. The reaction mixture was diluted with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium

chloride, dried and concentrated. The crude crystals were washed with diisopropyl ether to obtain the titled compound (0.947 g).

m.p.: 156-159°C.

Reference Example 78

[6-(4-Biphenylyl)methoxy-2-tetralin]-N-ethylacetamide

A mixture of [6-(4-biphenylyl)methoxy-2-tetralin]acetic acid (4.051 g, Reference Example 29), ethylamine hydrochloride (1.143 g), 1-hydroxybenzotriazole (1.647 g), WSC (2.536 g), and triethylamine (4.5 ml) in THF (80 ml) and acetonitrile (80 ml) was stirred at room temperature for one day. The reaction mixture was diluted with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried and concentrated. The crude crystals were washed with diisopropyl ether to obtain the titled compound (4.216 g).

m.p.: 168-172°C.

Reference Example 79

2-(4-Benzylpiperazin-1-yl)methyl-6-methoxytetralin dihydrochloride

2-Iodomethyl-6-methoxytetralin (1.209 g, Reference Example 8), 1-benzylpiperazine (0.852 g), and potassium carbonate (0.853 g) were added to DMF (15 ml). The reaction mixture was stirred at room temperature for 18 hr, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) and converted into its dihydrochloride, which was further

washed with diethyl ether to obtain the titled compound (1.217 g).

m.p.: 227-230°C (decomposed).

Reference Example 80

2-(4-Benzylpiperazin-1-yl)methyl-6-hydroxytetralin dihydrochloride

2-(4-Benzylpiperazin-1-yl)methyl-6-methoxytetralin dihydrochloride (0.849 g) was added to conc. hydrochloric acid (20 ml) and the reaction mixture was heated under reflux for 6 hr and cooled. The resulting precipitate was collected and washed with ethanol, methanol, and diethyl ether to obtain the titled compound (0.523 g).

m.p.: 230-236°C (decomposed).

Reference Example 81

Dimethyl (4-methoxy-2-nitrophenyl)methylidenemalonate

A mixture of 4-methoxy-2-nitrobenzaldehyde (21.3 g, Org. Synth., Vol. V, p-139, 1973), dimethyl malonate (16.5 g), piperidine (2.5 ml), and acetic acid (0.25 ml) in methanol (125 ml) was heated under reflux for 24 hr. The reaction mixture was concentrated, diluted with 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with 10% aqueous potassium carbonate and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate: hexane =1 : 2) to obtain the titled compound (25 g).

^{1}H NMR δ: 3.67 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 7.16 (1H, dd, J=8.8, 2.6 Hz), 7.36 (1H, d, J=8.8 Hz), 7.70 (1H, d, J=2.6 Hz), 8.14 (1H, s).

Reference Example 82

Dimethyl (4-methoxy-2-nitrobenzyl)malonate

To a solution of dimethyl (4-methoxy-2-nitrophenyl)methylidenemalonate (25 g) in methanol (200 ml) was added sodium borohydride (3.36 g) in an ice bath. After stirring at room temperature for 1 hr, the reaction mixture was neutralized by adding 1 N aqueous hydrochloric acid. The reaction mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate: hexane =1 : 4) to obtain the titled compound (19 g).

^{1}H NMR δ: 3.44 (2H, d, J=7.2 Hz), 3.71 (6H, s), 3.86 (3H, s), 3.80-4.00 (1H, m), 7.08 (1H, dd, J=10.8, 2.4 Hz), 7.28 (1H, d, J=10.8 Hz), 7.52 (1H, d, J=2.4 Hz).

Reference Example 83

1,2,3,4-Tetrahydro-7-methoxy-2-oxo-3-quinolinecarboxylic acid

A solution of dimethyl (4-methoxy-2-nitrobenzyl)malonate (19 g) in ethanol (200 ml) was hydrogenated in the presence of 10% palladium-C (2.0 g) at room temperature under one atmosphere of hydrogen for 24 hr. The reaction mixture was further stirred at 80° C for 24 hr and the catalyst was removed by filtration. The filtrate was concentrated. The residue was dissolved in the combined solvent of THF (250 ml) and methanol (250 ml) and 1 N aqueous sodium hydroxide (126 ml) was added in an ice bath. The reaction mixture was stirred at room temperature for 72 hr and concentrated. The residue was made acidic by

adding 1 N aqueous hydrochloric acid and the precipitate was collected by filtration. The crude crystals were washed with acetone to obtain the titled compound (11.7 g).

m.p.: 145-146°C (decomposed).

Reference Example 84

1,2,3,4-Tetrahydro-7-methoxy-N,N-dimethyl-2-oxo-3-quinolinecarboxamide

To a solution of 1,2,3,4-tetrahydro-7-methoxy-2-oxo-3-quinolinecarboxylic acid (3.74 g), dimethylamine hydrochloride (3.44 g), 1-hydroxybenzotriazole (2.85 g), and triethylamine (8.5 g) in acetonitrile (400 ml) was added WSC (6.5 g). The reaction mixture was stirred at room temperature for 24 hr and concentrated. The residue was diluted with ethyl acetate and the organic layer was washed with 1 N aqueous hydrochloric acid, 10% aqueous potassium carbonate, and saturated aqueous sodium chloride, dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the titled compound (1.63 g).

m.p.: 209-210°C.

Reference Example 85

3-(N,N-Dimethylamino)methyl-1,2,3,4-tetrahydro-7-methoxyquinoline dihydrochloride

To a solution of 1,2,3,4-tetrahydro-7-methoxy-N,N-dimethyl-2-oxo-3-quinolinecarboxamide (1.63 g) in THF (100 ml) was added 1M borane-THF complex (60 ml). The reaction mixture was heated under reflux for 24 hr. The reaction mixture was concentrated and the residue was heated under reflux with 6 N aqueous hydrochloric acid (30 ml) for 4 hr. The reaction mixture was made basic by adding 6 N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with 10% aqueous potassium carbonate, saturated

aqueous sodium chloride, dried, and concentrated. The residue was converted into its dihydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (1.27 g).

m.p.: 150-151°C.

Reference Example 86

3-(N,N-Dimethylamino)methyl-1,2,3,4-tetrahydro-7-quinolinol

A solution of 3-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydro-7-methoxyquinoline dihydrochloride (1.0 g) 48% hydrobromic acid (10 ml) was heated under reflux for 4 hr. The reaction mixture was poured into 10% aqueous potassium carbonate and extracted with ethyl acetate. The organic layer was dried and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the titled compound (0.81 g). The melting point of its dihydrochloride was 151-152°C. (recrystallizing solvent; methanol-diisopropyl ether).

Reference Example 87

Methyl 2,3,4,5-tetrahydro-8-methoxy-2-oxo-1H-1-benzazepine-4-carboxylate

Methyl 4-hydroxyimino-6-methoxytetralin-2-carboxylate (2.909 g, Journal of Medicinal Chemistry, 21, 1105-1110, 1978) was heated with polyphosphoric acid (30.22 g) at 100°C for 1.5 hr and cooled. Ice-water was added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to obtain the titled compound (2.125 g).

m.p.: 114-116°C.

Reference Example 88

2,3,4,5-Tetrahydro-8-methoxy-2-oxo-1*H*-1-benzazepine-4-carboxylic acid

To a solution of methyl 2,3,4,5-tetrahydro-8-methoxy-2-oxo-1H-1-benzazepine-4-carboxylate (5.035 g) in methanol (60 ml) was added 1 N aqueous sodium hydroxide (40 ml). The reaction mixture was stirred at room temperature for 6.5 hr, made acidic by adding 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The resulting crude crystals were washed with diethyl ether to obtain the titled compound (4.253 g).

m.p.: 202-204° C.

Reference Example 89

Methyl (1,2,3,4-tetrahydro-7-hydroxy-2-oxo-3-quinoline)acetate

2,3,4,5-Tetrahydro-8-methoxy-2-oxo-1H-1-benzazepine-4-carboxylic acid (4.013 g) was heated with 48% hydrobromic acid (40 ml) for 14 hr and cooled. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was dissolved in methanol (100 ml) and thionyl chloride (1.3 ml) was added to the solution at 0° C. After stirring for 3 hr, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The crude crystals were washed with diethyl ether to obtain the titled compound (3.239 g).

m.p.: 174-177° C.

Reference Example 90

Methyl [7-(4-biphenylyl)methoxy-1,2,3,4-tetrahydro-2-oxo-3-quinoline]acetate

A mixture of methyl [1,2,3,4-tetrahydro-7-hydroxy-2-oxo-3-quinoline]acetate (3.025 g), 4-chloromethylbiphenyl (2.864 g), and potassium carbonate (2.137 g) in DMF (80 ml) was stirred at room temperature for 5 days. The reaction mixture was diluted with water and extracted with a combined solvent of ethyl acetate and THF. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The resulting crude crystals were washed with ethyl acetate-hexane to obtain the titled compound (4.540 g).

m.p.: 174-178°C.

Reference Example 91

[7-(4-Biphenylyl)methoxy-1,2,3,4-tetrahydro-2-oxo-3-quinoline]acetic acid

To a solution of methyl [7-(4-biphenylyl)methoxy-1,2,3,4-tetrahydro-2-oxo-3-quinoline]acetate (2.475 g) in THF (60 ml) were added methanol (30 ml) and 1 N aqueous sodium hydroxide (12 ml). After stirring at room temperature for 2 days, the reaction mixture was made acidic by adding 1 N aqueous hydrochloric acid and extracted with combined solvent of ethyl acetate and THF. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The resulting crystals were washed with diisopropyl ether to obtain the titled compound (1.895 g).

m.p.: 193-206°C (decomposed).

Reference Example 92

[7-(4-Biphenylyl)methoxy-1,2,3,4-tetrahydro-2-oxo-3-quinoline]-N,N-dimethylacetamide

A mixture of [7-(4-biphenylyl)methoxy-1,2,3,4-

tetrahydro-2-oxo-3-quinoline]acetic acid (1.616 g), dimethylamine hydrochloride (0.674 g), 1-hydroxybenzotriazole (0.648 g), WSC (0.980 g), and N-methylmorpholine (2.0 ml) in THF (50 ml) and acetonitrile (50 ml) was stirred at room temperature for 2 days. The reaction mixture was diluted with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride and dried, and concentrated. The crude crystals were washed with diisopropyl ether to obtain the titled compound (1.557 g).

m.p.: 199-202°C.

Reference Example 93

N,N-Dimethyl-(6-hydroxy-1-oxo-2-tetralin)acetamide

A mixture of (6-hydroxy-1-oxo-2-tetralin)acetic acid (1.672 g, EP140684), dimethylamine hydrochloride (0.754 g), 1-hydroxybenzotriazole (1.468 g), and WSC (2.255 g), and triethylamine (3.1 ml) in THF (30 ml) and acetonitrile (30 ml) was stirred at room temperature for 36 hr. The reaction mixture was diluted with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried, and concentrated. The crude crystals were recrystallized from methanol-diisopropyl ether to obtain the titled compound (0.744 g).

m.p.: 181-186°C.

Reference Example 94

[6-(4-Biphenylyl)methoxy-1-oxo-2-tetralin]-N,N-dimethylacetamide

To a solution of N,N-dimethyl-(6-hydroxy-1-oxo-2-tetralin)acetamide (0.313 g), 4-chloromethylbiphenyl

(0.300g) in DMF (5 ml) was added sodium hydride (60% in oil, 80 mg) and the reaction mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate =2 : 1). The resulting crystals were washed with diisopropyl ether to obtain the titled compound (0.200 g).

m.p.: 131-135°C.

Reference Example 95

[6-(4-Biphenylyl)methoxy-2-(3,4-dihydronaphthalene)]-N,N-dimethylacetamide

To a solution of [6-(4-biphenylyl)methoxy-1-oxo-2-tetralin]-N,N-dimethylacetamide (0.954 g) in ethyl acetate (20 ml) and methanol (20 ml) was added sodium borohydride (0.175 g) at room temperature. After stirring at room temperature for 30 min, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was dissolved in toluene (30 ml) and heated under reflux in the presence of pyridinium p-toluenesulfonate (0.030 g) for 1.5 hr. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried, and concentrated. The resulting crystals were recrystallized from ethyl acetate-hexane to obtain the titled compound (0.779 g).

m.p.: 125-130°C.

Reference Example 96

6-(4-Biphenylyl)methoxy-2-[2-(imidazol-1-yl)ethyl]tetralin

The titled compound was synthesized using similar method as in Example 38.

m.p.: 145-146°C (recrystallizing solvent; ethyl acetate-hexane).

Reference Example 97

2-[6-(4-Biphenylyl)methoxy-2-tetralin]ethyl-N,N-dimethylamine oxide m-chlorobenzoate

6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1.269 g) was converted into its free form and dissolved in acetone (15 ml). 70% m-Chloroperbenzoic acid (0.777 g) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 25 min and precipitated crystals were collected by filtration. The crystals were washed with ethyl acetate and diethyl ether successively and recrystallized from THF-ethyl acetate to obtain the titled compound (0.811 g).

m.p.: 125-128°C.

Reference Example 98

2-[6-(4-Biphenylyl)methoxy-2-tetralin]ethyl-N,N-diethylamine oxide

6-(4-Biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin hydrochloride (134 mg) was converted into its free form and dissolved in acetone (5 ml). 70% m-Chloroperbenzoic acid (83 mg) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for one hr and diluted with 1 N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The crude product was recrystallized from ethyl acetate-hexane to obtain the titled compound (120 mg).

m.p.: 99-104°C.

Reference Example 99

(+)-6-(2-Bromopyridin-5-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin dihydrochloride

To a solution of (+)-2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (0.220 g) in DMF (5 ml) was added sodium hydride (60% in oil, 0.049 g) at room temperature. The reaction mixture was stirred at 50°C for 30 min. To the reaction mixture, cooled at 0°C, was added a solution of 2-bromo-5-pyridylmethylbromide (0.462g) in THF (5 ml). After stirring at 0°C for 2 hr, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4) and converted into its dihydrochloride, which was recrystallized from ethanol-ethyl acetate to obtain the titled compound (295 mg).

m.p.: 171-181°C (decomposed).

$[\alpha]_D^{20}$=+41.2° (c=0.500 in methanol).

Reference Example 100

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide hydrochloride

6-Amino-2-(N,N-dimethylamino)methyltetralin (0.216 g; obtained in Reference Example 32) was dissolved in pyridine (10 ml), to which was added 4-biphenylcarbonyl chloride (0.311 g). The reaction mixture was stirred at room temperature for 12 hours, pyridine was evaporated out under reduced pressure, and water was added to the resulting residue, which was then extracted with ethyl acetate. The organic layer was

washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/1), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-ethyl acetate to obtain the entitled compound (0.224 g).

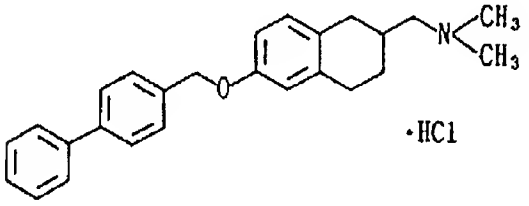
m.p.: >250° C.

^{1}H NMR δ: 1.24-1.54(1H,m), 1.84-2.10(2H,m), 2.20-2.50(3H,m), 2.26(6H,s), 2.79-3.01(3H,m), 7.10(1H,d,J=8Hz), 7.28-7.54(5H,m), 7.60-7.82(5H,m), 7.94(2H,d,J=8Hz).

IR (KBr): 3028, 2910, 2640, 1658, 1538, 1417, 746, 701 cm^{-1}.

Example 1

6-(4-Biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin hydrochloride



2-(N,N-Dimethylamino)methyl-6-hydroxytetralin (0.151 g, free base of the compound obtained in Reference Example 16) was dissolved in DMF (5 ml), to which was added 60% oily sodium hydride (92 mg) at 0°C. The reaction mixture was warmed to room temperature, and then stirred for 30 minutes. This was again cooled to 0°C, to which was added 4-(chloromethyl)biphenyl (0.183 g) and stirred at room temperature for 3 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was

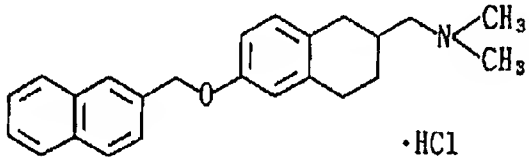
washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1 to ethyl acetate/methanol = 10/1), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diethyl ether to obtain the entitled compound (0.210 g).

m.p.: 229-233°C.

Compounds of the following Examples 2 to 11 were obtained in the same manner as in Example 1.

Example 2

2-(N,N-Dimethylamino)methyl-6-(2-naphthyl)methoxytetralin hydrochloride

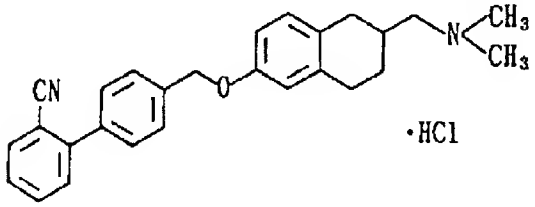


m.p.: 228-229°C.

Solvent for recrystallization: methanol-ethyl acetate

Example 3

6-(2'-Cyanobiphenyl-4-yl)methoxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

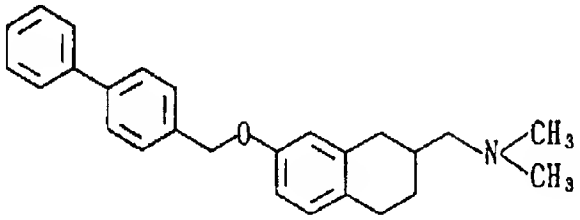


m.p.: 202-203°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 4

7-(4-Biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin hydrochloride



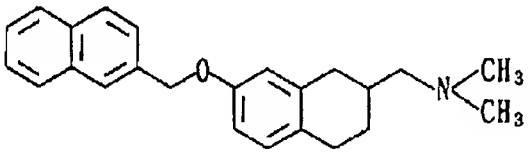
·HCl

m.p.: 232-233°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 5

2-(N,N-Dimethylamino)methyl-7-(2-naphthyl)methoxytetralin hydrochloride



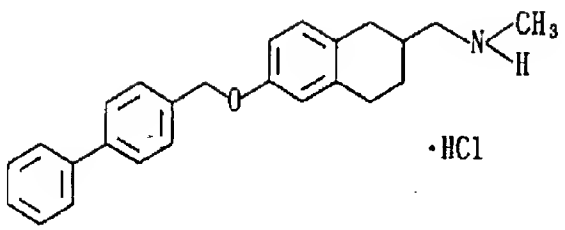
·HCl

m.p.: 201-202°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 6

6-(4-Biphenylyl)methoxy-2-(N-methylamino)methyltetralin hydrochloride

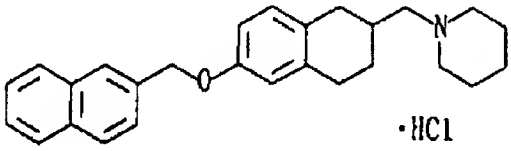


m.p.: 189-190°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 7

6-(2-Naphthyl)methoxy-2-piperidinomethyltetralin hydrochloride

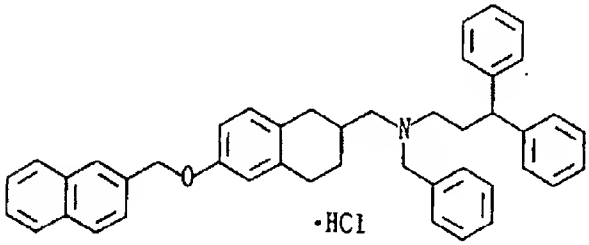


m.p.: 215-218°C (decomposed).

Solvent for recrystallization: methanol-diethyl ether

Example 8

2-[N-Benzyl-N-(3,3-diphenylpropyl)amino]methyl-6-(2-naphthyl)methoxytetralin hydrochloride



This was amorphous powder.

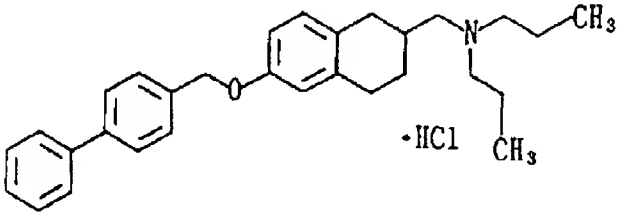
^{1}H NMR δ: 1.12-1.36(1H,m), 1.70-2.05(2H,m), 2.13-2.48(7H,m), 2.61-2.89(3H,m), 3.55(2H,d,J=2Hz),

3.98(1H,t,J=8Hz), 5.18(2H,s), 6.69-6.81(2H,m), 6.96(1H,d,J=8Hz), 7.04-7.34(15H,m), 7.41-7.56(3H,m), 7.78-7.90(4H,m).

IR (KBr): 3058, 3028, 2925, 2578, 1602, 1500, 1452, 1270, 1232, 747, 701 cm^{-1}.

Example 9

6-(4-Biphenylyl)methoxy-2-(N,N-dipropylamino)methyltetralin hydrochloride

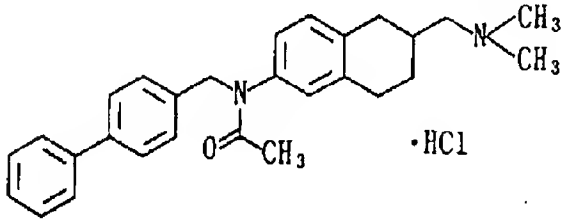


m.p.: 164-166° C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 10

6-[N-Acetyl-N-(4-biphenylyl)methyl]amino-2-(N,N-dimethylamino)methyltetralin hydrochloride

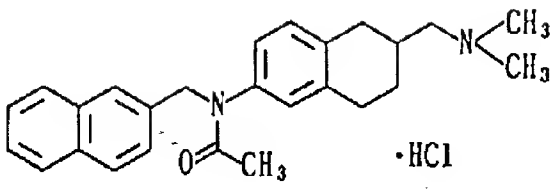


Solvent for recrystallization: methanol-ethyl acetate

m.p.: 179-182° C.

Example 11

6-[N-Acetyl-N-(2-naphthyl)methyl]amino-2-(N,N-dimethylamino)methyltetralin hydrochloride



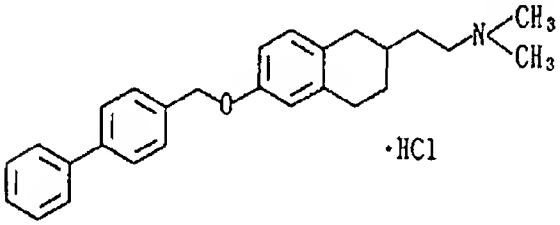
This was amorphous powder.

^{1}H NMR δ: 1,20-1.45(1H,m), 1.76-2.00(2H,m), 1.93(3H,s), 2.08-2.44(3H,m), 2.24(6H,s), 2.64-2.76(2H,m), 2.82-2.96(1H,m), 5.02(2H,s), 6.64-6.76(2H,m), 6.98(1H,d,J=8Hz), 7.36-7.50(3H,m), 7.61(1H,br,s), 7.70-7.86(3H,m).

IR (KBr): 3394, 2929, 2669, 1648, 1500, 1401, 1295, 821, 757 cm^{-1}.

Example 12

6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



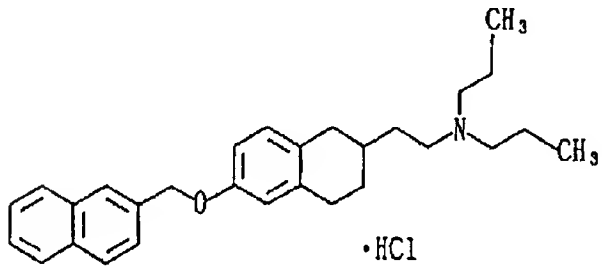
[6-(4-Biphenylyl)methoxy-2-tetralin]-N,N-dimethylacetamide (1.497 g; obtained in Reference Example 30) was dissolved in anhydrous THF (20 ml), to which was added lithium aluminum hydride (0.222 g). The reaction mixture was stirred at room temperature for 40 minutes, and then heated under reflux for 40 minutes. This was left cooled, and water was added thereto, from which were removed insoluble substances through filtration. The filtrate was concentrated. The residue was purified by silica gel column

chromatography (eluent: ethyl acetate/hexane = 1/1 to ethyl acetate alone to ethyl acetate/methanol = 10/1), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (1.022 g).

m.p.: 223-226°C (decomposed).

Example 13

2-[2-(N,N-Dipropylamino)ethyl]-6-(2-naphthyl)methoxytetralin hydrochloride

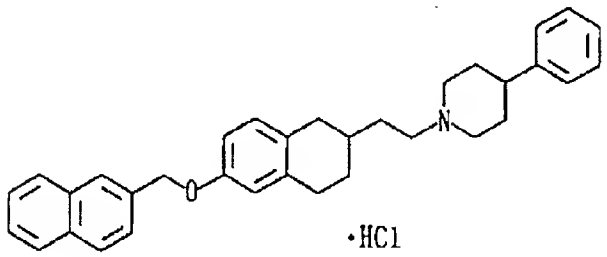


2-(2-Iodoethyl)-6-(2-naphthyl)methoxytetralin (0.193 g; obtained in Reference Example 27) was dissolved in DMF (5 ml), to which were added N,N-dipropylamine (0.09 ml) and anhydrous potassium carbonate (0.135 g). The reaction mixture was stirred at room temperature for 5 hours, and water was added thereto, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1 to ethyl acetate/methanol = 10/1), and the processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from ethyl acetate-diisopropyl ether to obtain the entitled compound (0.105 g).

m.p.: 146-148°C.

Example 14

6-(2-Naphthyl)methoxy-2-[2-(4-phenylpiperidino)ethyl]tetralin hydrochloride



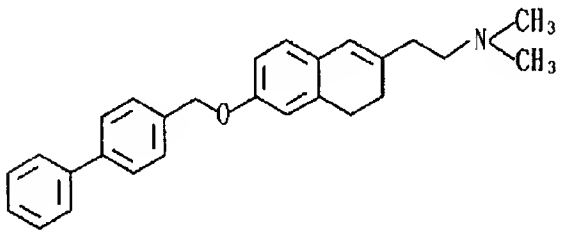
The entitled compound was obtained in the same manner as in Example 13.

m.p.: 229-234° C (decomposed).

Solvent for recrystallization: methanol-diisopropyl ether

Example 15

6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]-3,4-dihydronaphthalene



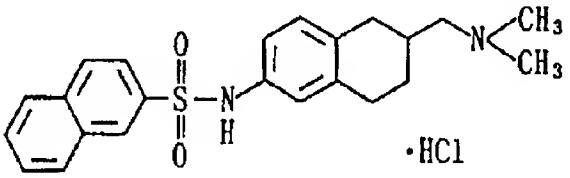
To a solution of [6-(4-biphenylyl)methoxy-2-(3,4-dihydronaphthalene)]-N,N-dimethylacetamide (205 mg) in THF (10 ml) was added lithium aluminum hydride (20 mg) at 0° C. The reaction mixture was diluted with water and the precipitate was removed by filtration. The filtrate was concentrated and the residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4). The crude crystals were recrystallized from ethyl acetate-hexane to obtain the

titled compound (46 mg).

m.p.: 123-126°C.

Example 16

N-[2-(N,N-Dimethylamino)methyltetralin-6-yl]-2-naphthalenesulfonamide hydrochloride



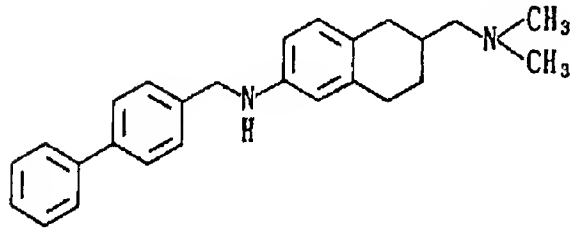
The entitled compound was obtained in the same manner as in Reference Example 100. This was amorphous powder.

^{1}H NMR δ: 1.16-1.40(1H,m), 1.72-1.97(2H,m), 2.08-2.38(3H,m), 2.21(6H,s), 2.60-2.90(3H,m), 6.74-6.84(2H,m), 6.90(1H,d,J=8Hz), 7.52-7.68(2H,m), 7.72(1H,dd,J=9Hz,2Hz), 7.82-7.94(3H,m), 8.36(1H,br,s).

IR (KBr): 3394, 2927, 2698, 1614, 1504, 1320, 1156, 962, 821, 751, 657 cm^{-1}.

Example 17

6-[N-(4-Biphenylyl)methyl]amino-2-(N,N-dimethylamino)methyltetralin



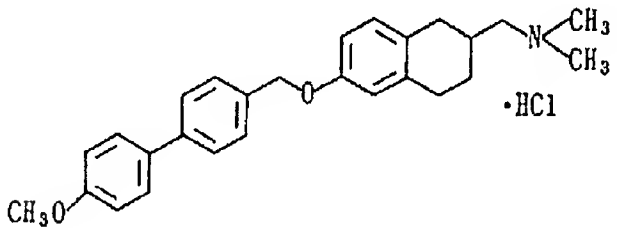
1 M Borane-THF complex (2 ml) was added to a THF solution (3 ml) of N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide (0.172 g; free base

of the compound of Reference Example 100), and the reaction mixture was heated under reflux for 1 hour. Water was added to this, and then 6 N hydrochloric acid was added thereto, and stirred at room temperature for 1 hour. Then, the reaction mixture was made basic with an aqueous solution of 1 N sodium hydroxide added thereto, and thereafter extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The concentrate was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/4), and then recrystallized from ethyl acetate-hexane to obtain the entitled compound (0.060 g).

m.p.: 106-108°C.

Example 18

2-(N,N-Dimethylamino)methyl-6-(4'-methoxybiphenyl-4-yl)methoxytetralin hydrochloride



6-(4-Bromobenzyl)oxy-2-(N,N-dimethylamino)methyltetralin (374 mg; obtained in Reference Example 33) and tetrakis-(triphenylphosphine) palladium (35 mg) were dissolved in toluene (8 ml), to which were added an ethanol solution (1 ml) of 4-methoxyphenylboric acid (198 mg) and an aqueous 2 M sodium carbonate solution (1 ml). The reaction mixture was heated under reflux for 6 hours in an argon atmosphere. A saturated aqueous sodium chloride solution was added to this, which was then extracted with ethyl acetate. The organic layer was dried, and

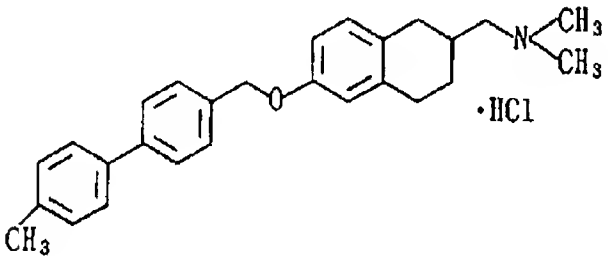
then concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/10), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from ethanol-ethyl acetate to obtain the entitled compound (0.290 g).

m.p.: 210-211°C.

Compounds of the following Examples 19 to 35 were obtained in the same manner as in Example 18.

Example 19

2-(N,N-Dimethylamino)methyl-6-(4'-methylbiphenyl-4-yl)methoxytetralin hydrochloride

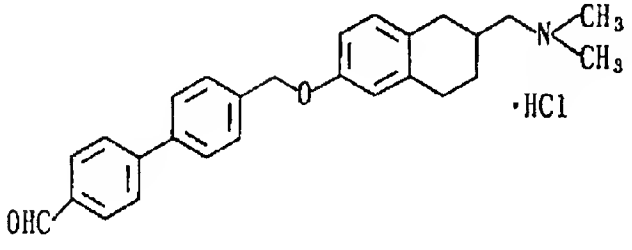


m.p.: 226-228°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 20

2-(N,N-Dimethylamino)methyl-6-(4'-formylbiphenyl-4-yl)methoxytetralin hydrochloride



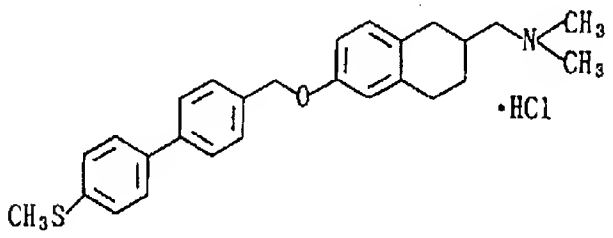
m.p.: 234-235°C.

Solvent for recrystallization: ethanol-ethyl

acetate

Example 21

2-(N,N-Dimethylamino)methyl-6-(4'-methylthiobiphenyl-4-yl)methoxytetralin hydrochloride

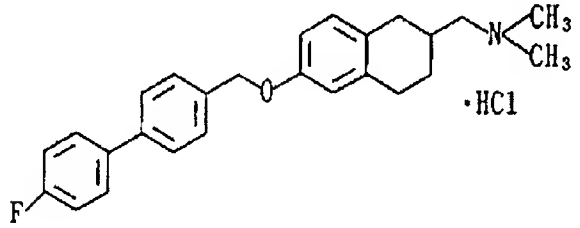


m.p.: 235-237°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 22

2-(N,N-Dimethylamino)methyl-6-(4'-fluorobiphenyl-4-yl)methoxytetralin hydrochloride

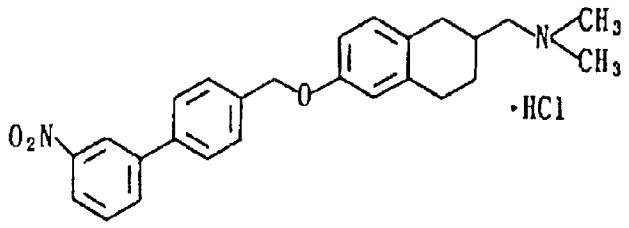


m.p.: 223-234°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 23

2-(N,N-Dimethylamino)methyl-6-(3'-nitrobiphenyl-4-yl)methoxytetralin hydrochloride

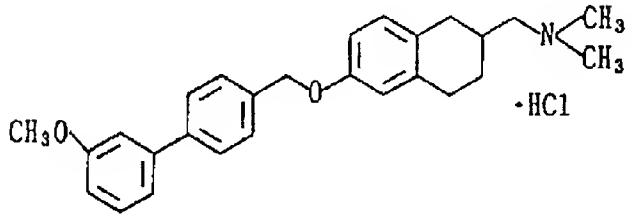


m.p.: 223-234°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 24

2-(N,N-Dimethylamino)methyl-6-(3'-methoxybiphenyl-4-yl)methoxytetralin hydrochloride

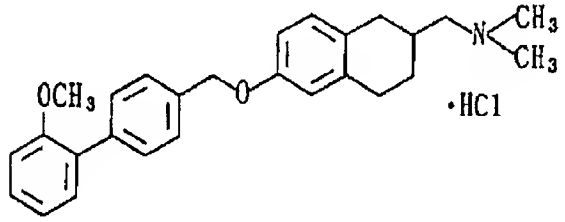


m.p.: 207-208°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 25

2-(N,N-Dimethylamino)methyl-6-(2'-methoxybiphenyl-4-yl)methoxytetralin hydrochloride

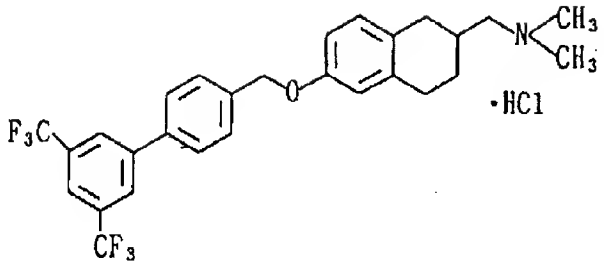


m.p.: 140-141°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 26

2-(N,N-Dimethylamino)methyl-6-[3',5'-bis(trifluoromethyl)biphenyl-4-yl]methoxytetralin hydrochloride

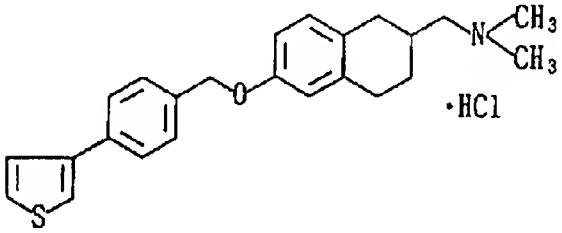


m.p.: 196-197°C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 27

2-(N,N-Dimethylamino)methyl-6-[4-(3-thienyl)benzyl]oxytetralin hydrochloride

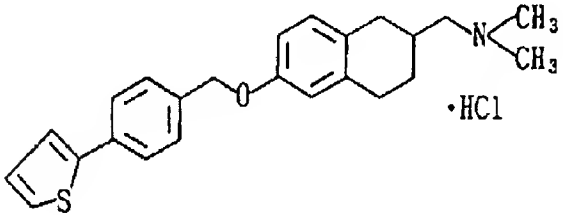


m.p.: 222-223°C.

Solvent for recrystallization: ethanol-ethyl acetate.

Example 28

2-(N,N-Dimethylamino)methyl-6-[4-(2-thienyl)benzyl]oxytetralin hydrochloride

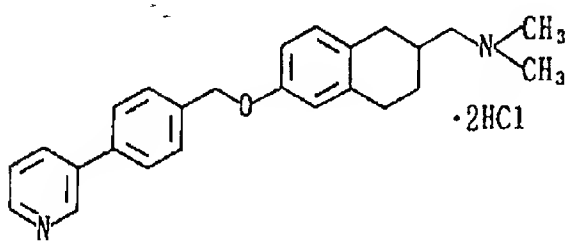


m.p.: 227-228°C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 29

2-(N,N-Dimethylamino)methyl-6-[4-(3-pyridyl)benzyl]oxytetralin dihydrochloride

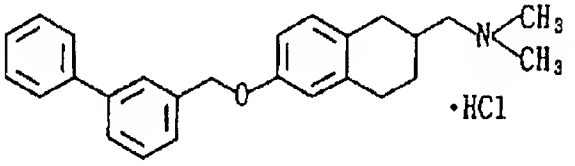


m.p.: 212-213° C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 30

6-(3-Biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

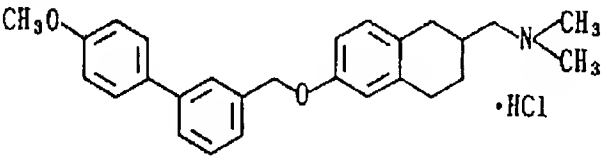


m.p.: 186-190° C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 31

2-(N,N-Dimethylamino)methyl-6-(4'-methoxybiphenyl-3-yl)methoxytetralin hydrochloride



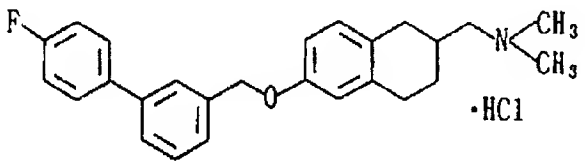
m.p.: 182-183° C.

Solvent for recrystallization: ethanol-ethyl

acetate

Example 32

2-(N,N-Dimethylamino)methyl-6-(4'-fluorobiphenyl-3-yl)methoxytetralin hydrochloride

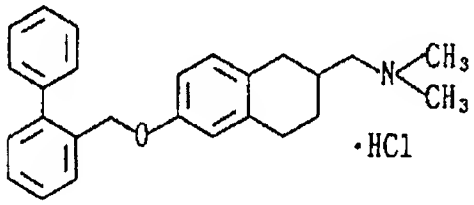


m.p.: 171-172° C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 33

6-(2-Biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin hydrochloride

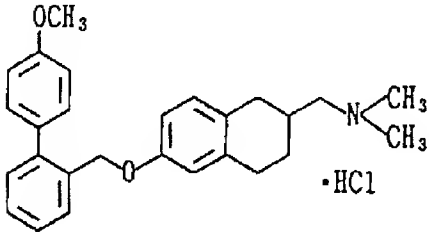


m.p.: 173-174° C.

Solvent for recrystallization: ethanol-ethyl acetate

Example 34

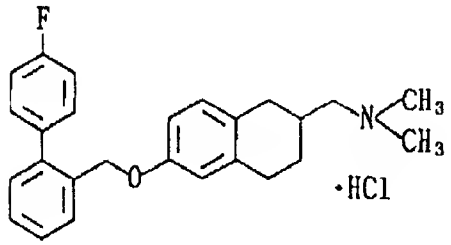
2-(N,N-Dimethylamino)methyl-6-(4'-methoxybiphenyl-2-yl)methoxytetralin hydrochloride



m.p.: 170-171°C.
Solvent for recrystallization: ethanol-ethyl acetate

Example 35

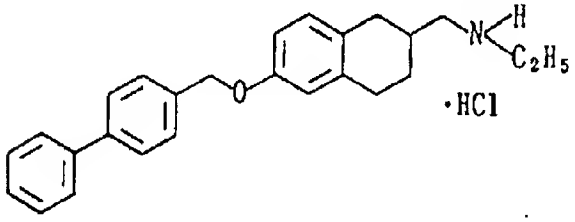
2-(N,N-Dimethylamino)methyl-6-(4'-fluorobiphenyl-2-yl)methoxytetralin hydrochloride



m.p.: 172-174°C.
Solvent for recrystallization: ethanol-ethyl acetate

Example 36

6-(4-Biphenylyl)methoxy-2-(N-ethylamino)methyltetralin hydrochloride



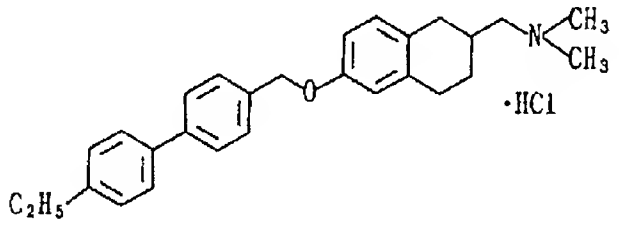
N-[6-(4-Biphenylyl)methoxy-2-tetralinyl)]methylacetamide (500 mg; obtained in Reference Example 23) was dissolved in THF (10 ml), to which was added lithium aluminum hydride (50 mg), and stirred at room temperature for 1 hour. An aqueous solution of sodium potassium tartrate was added to the reaction mixture with cooling with ice, from which were removed insoluble substances through filtration, and

the filtrate was concentrated. The residue was processed with 4 N hydrochloric acid-ethyl acetate, and then recrystallized from ethanol-diisopropyl ether to obtain the entitled compound (0.138 g).

m.p.: 229-230°C.

Example 37

2-(N,N-Dimethylamino)methyl-6-(4'-ethylbiphenyl-4-yl)methoxytetralin hydrochloride

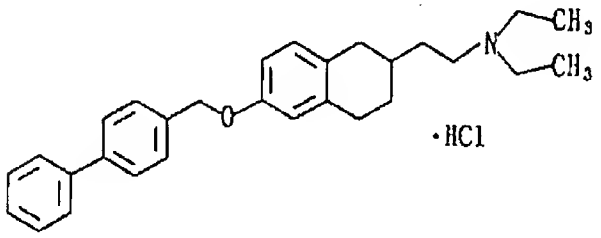


2-(N,N-Dimethylamino)methyl-6-hydroxytetralin (300 mg; obtained in Reference Example 16), (4'-ethylbiphenyl-4-yl)methanol (372 mg) and triphenylphosphine (460 mg) were dissolved in THF (5 ml), to which was dropwise added diethyl azodicarboxylate (305 mg) with cooling with ice. The reaction mixture was stirred at room temperature for 4 hours, and then the solvent was evaporated out. Water was added to the residue, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/10), and then processed with a solution of 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from ethanol-diisopropyl ether to obtain the entitled compound (310 mg).

m.p.: 229-230°C.

Example 38

6-(4-Biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin hydrochloride



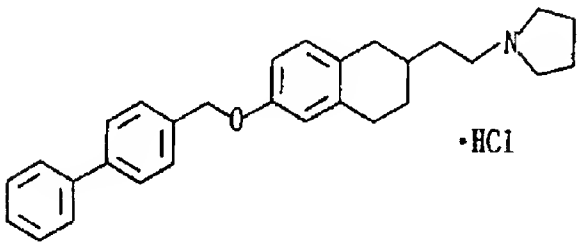
6-(4-Biphenylyl)-2-(2-iodoethyl)methoxytetralin (2.50 g), diethylamine (1.03 g) and potassium carbonate (1.95 g) were added to DMF (20 ml). The reaction mixture was stirred at room temperature for 24 hours, to which water was added. The crystals thus formed were taken out through filtration, then washed with ethyl acetate, and recrystallized from ethanol-diisopropyl ether. The crystals were processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from ethanol-diisopropyl ether to obtain the entitled compound (1.53 g).

m.p.: 141-143°C.

Compounds of the following Examples 39 to 42 were obtained in the same manner as in Example 38.

Example 39

6-(4-Biphenylyl)methoxy-2-[2-(pyrrolidin-1-yl)ethyl]tetralin hydrochloride

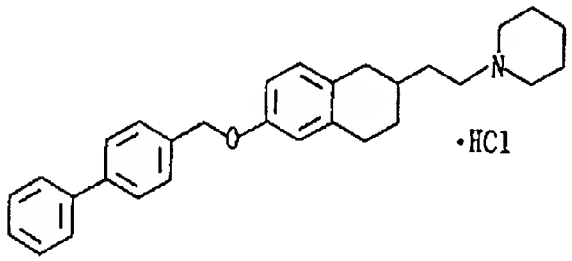


m.p.: 197-199°C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 40

6-(4-Biphenylyl)methoxy-2-(2-piperidinoethyl)tetralin hydrochloride

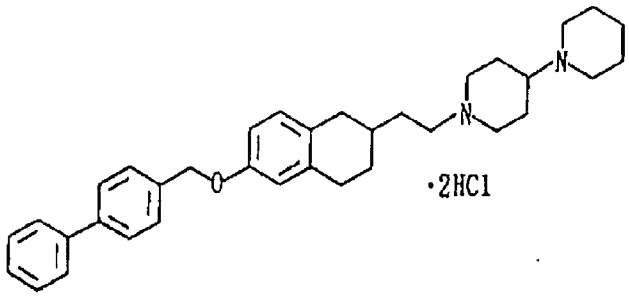


m.p.: 196-198°C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 41

6-(4-Biphenylyl)methoxy-2-[2-(4-piperidinopiperidino)ethyl]tetralin dihydrochloride

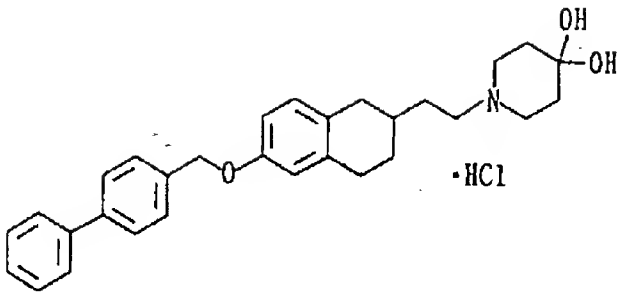


m.p.: 288-291°C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 42

6-(4-Biphenylyl)methoxy-2-[2-(4,4-dihydroxypiperidino)ethyl]tetralin hydrochloride

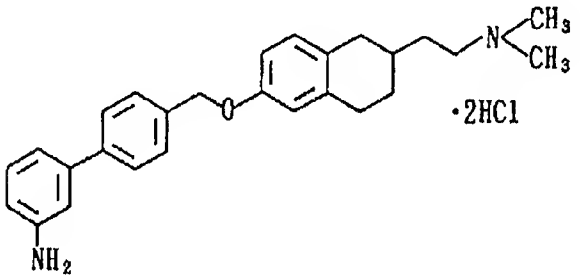


m.p.: 155-156°C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 43

6-(3'-Aminobiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



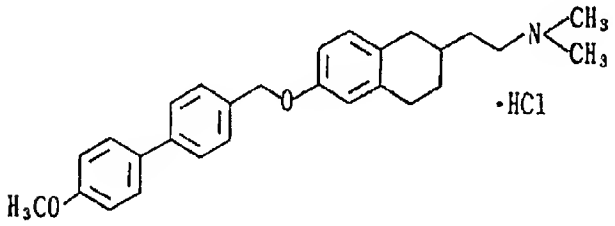
An ethanol solution (10 ml) of 3-aminophenylboric acid (1.3 g) and an aqueous 2M sodium carbonate solution (10 ml) were added to a toluene solution (80 ml) of 6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin (3.00 g) and tetrakis-(triphenylphosphine) palladium (0.45 g). The reaction mixture was heated under reflux for 12 hours in an argon atmosphere. A saturated aqueous sodium chloride solution was added to this, which was then extracted with ethyl acetate. The organic layer was dried, and then concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane =

1/2), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.78 g).

m.p.: 205-206° C.

Example 44

2-[2-(N,N-Dimethylamino)ethyl]-6-[(4'-methoxybiphenyl-4-yl)methoxy]tetralin hydrochloride



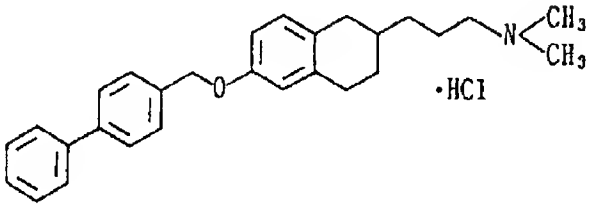
The entitled compound was obtained in the same manner as in Example 43.

m.p.: 182-185° C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 45

6-(4-Biphenylyl)methoxy-2-[3-(N,N-dimethylamino)propyl]tetralin hydrochloride



60% Oily sodium hydride (0.258 g) was added to a DMF solution (20 ml) of 2-[3-(N,N-dimethylamino)propyl]-6- hydroxytetralin (1.00 g) at

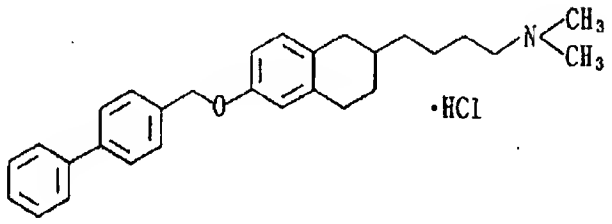
0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. This was again cooled to 0°C, and 4-(chloromethyl)biphenyl (1.04 g) as added thereto, and then stirred at room temperature for 4 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: toluene alone to toluene/ethyl acetate =1/1), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (1.30 g).

m.p.: 161-163° C.

Example 46

6-(4-Biphenylyl)methoxy-2-[4-(N,N-dimethylamino)butyl]tetralin hydrochloride

The entitled compound was obtained in the same manner as in Example 45.



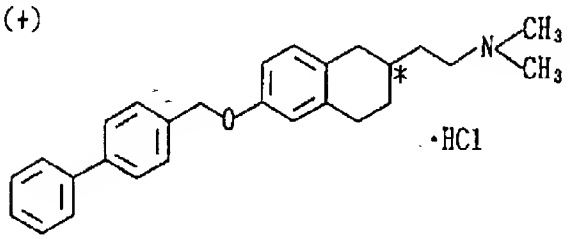
m.p.: 175-177° C.

Solvent for recrystallization: methanol-diisopropyl ether

Example 47

(+)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-

dimethylamino)ethyl]tetralin hydrochloride



(+)-2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin hydrochloride (0.424 g) was converted into its free form, and then dissolved in DMF (10 ml), to which was added 60% oily sodium hydroxide (0.106 mg) at room temperature, and stirred for 45 minutes. The reaction mixture was heated up to 50°C, and stirred for 45 minutes. This was then cooled to 0°C, to which was added a DMF solution (5 ml) of 4-(chloromethyl)biphenyl (0.367 g), and stirred at room temperature for 2 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/10 to 1/4), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.484 g).

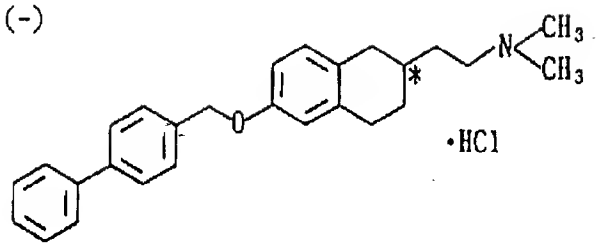
m.p.: 220-226°C (decomposed).

$[\alpha]_D^{20}$ = +46.0° (c = 0.54, methanol)

Optical purity: not lower than 99% e.e.

Example 48

(-)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



(-)-2-(N,N-dimethylamino)ethyl-6-hydroxytetralin hydrochloride (0.437 g) was converted into its free form, and then dissolved in DMF (10 ml), to which was added 60% oily sodium hydroxide (0.122 mg) at room temperature. The reaction mixture was heated up to 50°C, and stirred for 1 hour. This was then cooled to 0°C, to which was added a DMF solution (5 ml) of 4-(chloromethyl)biphenyl (0.344 g), and stirred at room temperature for 2 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, then dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate/hexane = 1/10 to 1/4), and then processed with 4 N hydrochloric acid-ethyl acetate to form a hydrochloride. The thus-formed salt was recrystallized from methanol-diisopropyl ether to obtain the entitled compound (0.471 g).

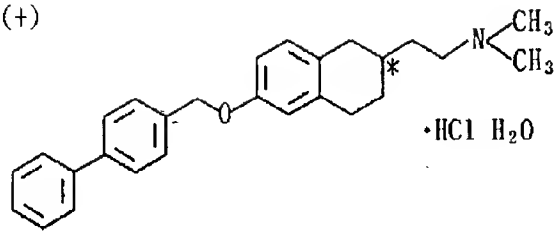
m.p.: 219-225°C (decomposed).

$[\alpha]_D^{20}$ = -45.2° (c = 0.52, methanol)

Optical purity: not lower than 99% e.e.

Example 49

(+)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride monohydrate



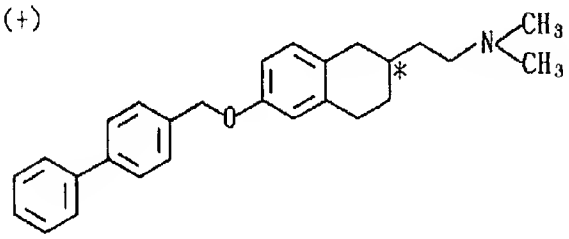
(+)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (150 g) was recrystallized from ethanol (2000 ml)-water (60 ml) to obtain the titled compound (127 g).

m.p.: 215-217°C (decomposed).

$[\alpha]_D^{20}$=+42.4° (c=1.00 in methanol).

Example 50

(+)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin



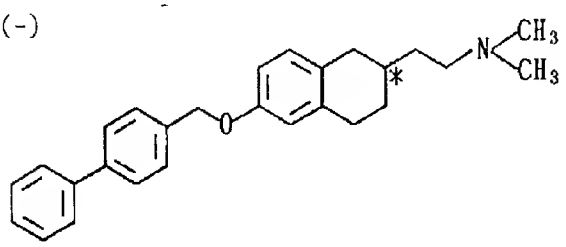
(+)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (4.50 g) was partitioned between ethyl acetate and 10% aqueous potassium carbonate and extracted. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was recrystallized from ethanol to obtain the titled compound (3.60 g).

m.p.: 83.5-84.5°C.

$[\alpha]_D^{20}$=+51.7° (c=1.00 in methanol).

Example 51

(-)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin



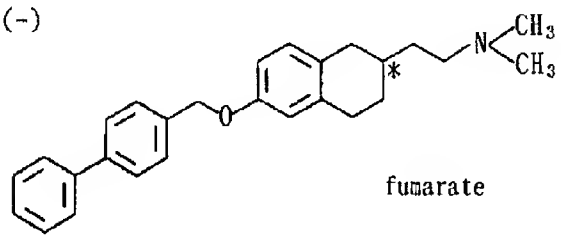
(-)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (3.00 g) was partitioned between ethyl acetate and 10% aqueous potassium carbonate and extracted. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was recrystallized from ethanol to obtain the titled compound (2.20 g).

m.p.: 84.2-85.2°C.

$[\alpha]_D^{20}$=-50.1° (c=0.50 in methanol).

Example 52

(-)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin fumarate



To a solution of (-)-6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin (1.3 g) in methanol (10 ml) was added a solution of fumaric acid (0.39 g) in methanol (10 ml) and concentrated. The resulting

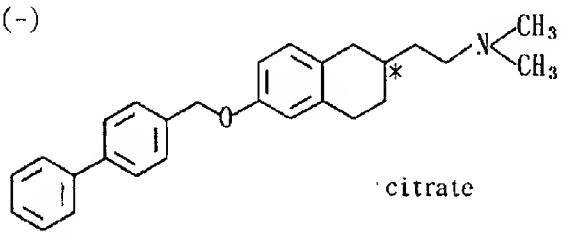
salt was recrystallized from methanol to obtain the titled compound (0.7 g).

m.p.: 212-213°C (decomposed).

$[\alpha]_D^{20}$=-40.4° (c=0.5 in methanol).

Example 53

(-)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin citrate

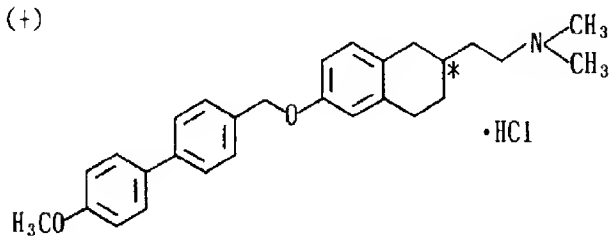


To a solution of (-)-6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin (1.3 g) in methanol (10 ml) was added a solution of citric acid (0.65 g) in methanol (10 ml) and the resulting precipitated salt was collected by filtration and washed with methanol, ethyl acetate, and diethyl ether to obtain the titled compound (1.9 g).

m.p.: 185-186°C (decomposed).

Example 54

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-(4'-methoxybiphenyl-4-yl)methoxytetralin hydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-

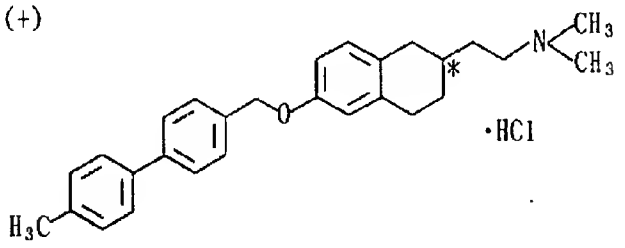
dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 4-Methoxybenzeneboric acid (465 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 50 to 1 : 4) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (870 mg).

m.p.: 230-232° C (decomposed).

$[\alpha]_D^{20}$=+39.2° (c=1.00 in methanol).

Example 55

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-(4'-methylbiphenyl-4-yl)methoxytetralin hydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 4-Methylbenzeneboric acid (416 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under

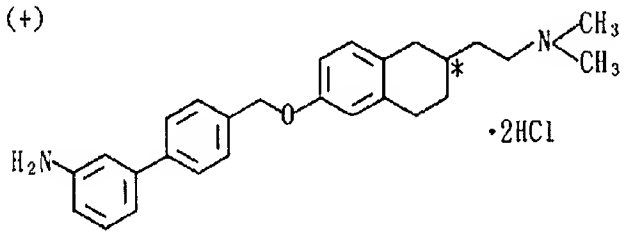
reflux for 5 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane=1 : 40 to 1 : 4) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (660 mg).

m.p.: 225-227°C (decomposed).

$[\alpha]_D^{20}$=+44.0° (c=1.00 in methanol).

Example 56

(+)-6-(3'-Aminobiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin dihydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 3-Aminobenzeneboric acid (474 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina

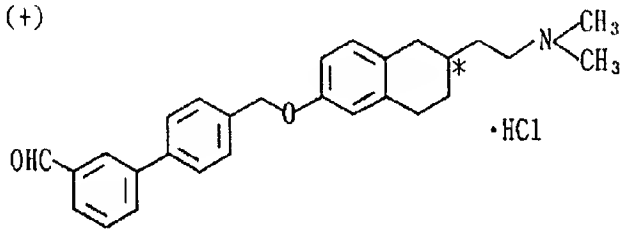
column chromatography (eluent: ethyl acetate : hexane=1:20 to 1:2) and converted into its dihydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (830 mg).

m.p.: 210-211°C (decomposed).

$[\alpha]_D^{20}$=+38.3° (c=1.00 in methanol).

Example 57

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-(3'-formylbiphenyl-4-yl)methoxytetralin hydrochloride



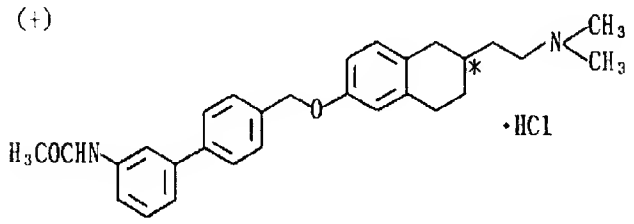
A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 3-Formylbenzeneboric acid (460 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1: 20 to 1: 2) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (590 mg).

m.p.: 194-196°C (decomposed).

$[\alpha]_D^{20}$=+44.0° (c=1.00 in methanol).

Example 58

(+)-6-(3'-Acetamidobiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



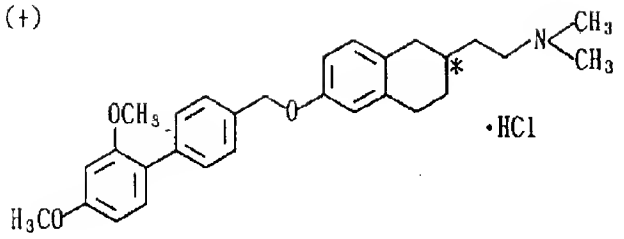
A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 3-Acetamidobenzeneboric acid (559 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 6 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The resultant crude crystals were washed with ethyl acetate and diisopropyl ether, purified by alumina column chromatography (eluent: ethyl acetate) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (610 mg).

m.p.: 198-200°C (decomposed).

$[\alpha]_D^{20}$=+41.0° (c=0.50 in methanol).

Example 59

(+)-6-(2',4'-Dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



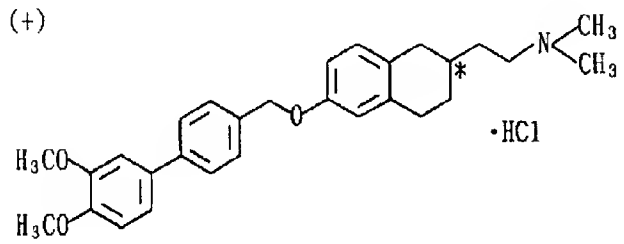
A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 2.4-Dimethoxybenzeneboric acid (557 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1: 20 to 1: 5) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (740 mg).

m.p.: 159-161°C.

$[\alpha]_D^{20}$=+42.2° (c=0.50 in methanol).

Example 60

(+)-6-(3',4'-Dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



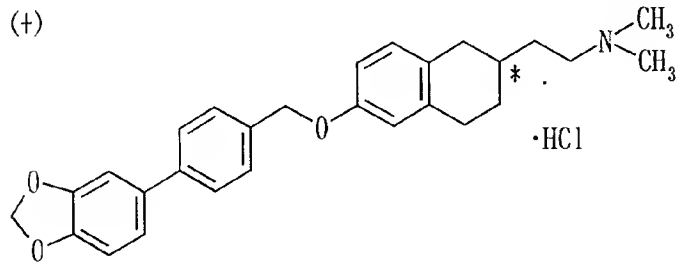
A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 3.4-Dimethoxybenzeneboric acid (557 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 5 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1: 20 to 1: 5) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (840 mg).

m.p.: 228-230°C (decomposed).

$[\alpha]_D^{20}$=+42.2° (c=0.50 in methanol).

Example 61

(+)-6-[4-(1,3-Benzodioxol-5-yl)phenyl]methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N, N-dimethylamino) ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room

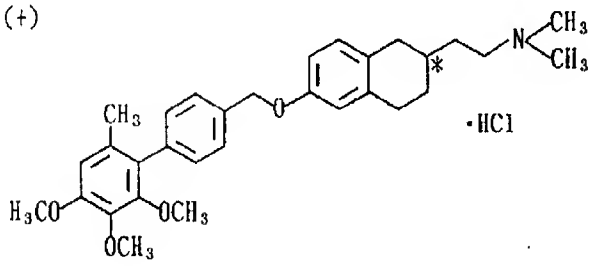
temperature for 10 min. 3,4-Methylenedioxybenzeneboric acid (469 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1: 20 to 1: 5) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (830 mg).

m.p.: 222-224°C (decomposed).

$[\alpha]_D^{20}$=+39.9° (c=0.40 in methanol).

Example 62

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-(2',3',4'-trimethoxy-6'-methylbiphenyl-4-yl)methoxytetralin hydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. To the reaction mixture were added 2,3,4-trimethoxy-6-methylbenzeneboric acid (692 mg) and tetrakis(triphenylphosphine) palladium (82 mg)

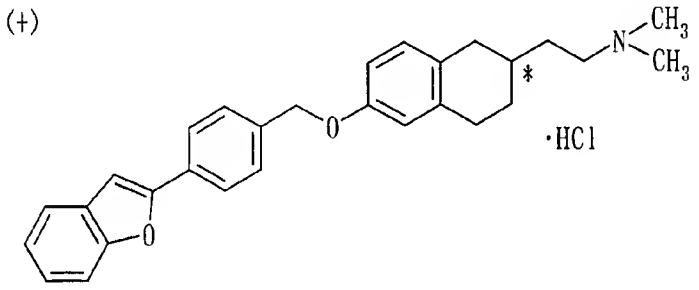
and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 20 to 1 : 6) and converted into its hydrochloride, which was recrystallized from methanol-diisopropyl ether to obtain the titled compound (950 mg).

m.p.: 222-224°C (decomposed).

$[\alpha]_D^{20}$=+37.7° (c=0.50 in methanol).

Example 63

(+)-6-[4-(2-Benzofuranyl)phenyl]methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml) and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 2-Benzofuranboric acid (496 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 6 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with

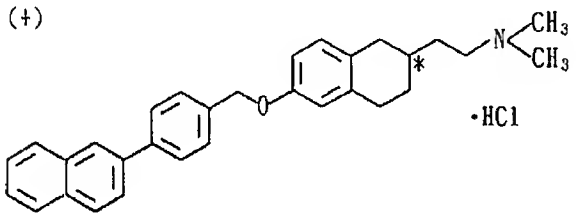
saturated aqueous sodium chloride, dried, and concentrated. The crude crystals were washed with diisopropyl ether and further purified by alumina column chromatography (eluent: ethyl acetate) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl ether to obtain the titled compound (730 mg).

m.p.: 235-237°C (decomposed).

$[\alpha]_D^{20}$=+42.2° (c=0.40 in methanol).

Example 64

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-[4-(2-naphthyl)phenyl]methoxytetralin hydrochloride



A mixture of (+)-6-(4-bromobenzyl)oxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride (1 g), toluene (20 ml), ethanol (2.5 ml), and 2 M aqueous sodium carbonate (2.5 ml) was stirred at room temperature for 10 min. 2-Naphthaleneboric acid (526 mg) and tetrakis(triphenylphosphine) palladium (82 mg) were added and the reaction mixture was heated under reflux for 14 hr under argon. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 20 to 1 : 7) and converted into its hydrochloride, which was then recrystallized from methanol-diisopropyl

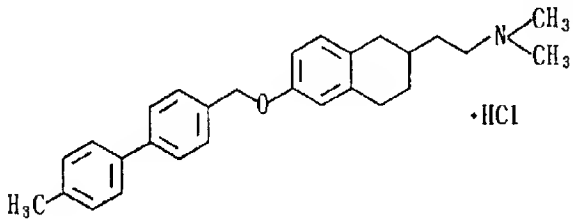
ether to obtain the titled compound (850 mg).

m.p.: 233-235°C (decomposed).

$[\alpha]_D^{20}$=+40.6° (c=0.40 in methanol).

Example 65

2-[2-(N,N-Dimethylamino)ethyl]-6-[(4'-methylbiphenyl-4-yl)methoxy]tetralin hydrochloride



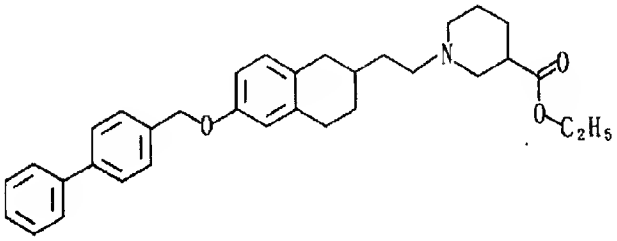
The titled compound was synthesized by the similar manner as in Example 43.

m.p.: 208-209°C.

Recrystallizing solvent: ethanol.

Example 66

6-(4-Biphenylyl)methoxy-2-[2-(3-ethoxycarbonylpiperidino)ethyl]tetralin



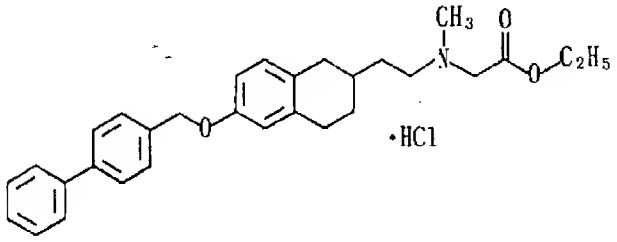
The titled compound was synthesized by the similar manner as in Example 38.

m.p.: 97-98°C.

Recrystallizing solvent: ethyl acetate - hexane.

Example 67

6-(4-Biphenylyl)methoxy-2-[(3-aza-4-ethoxycarbonyl-3-methyl)butyl]tetralin hydrochloride



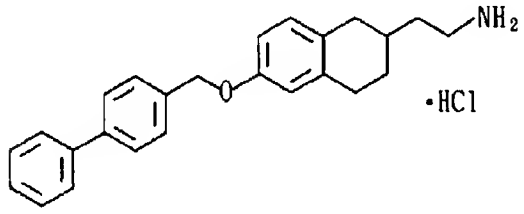
The titled compound was synthesized by the similar manner as in Example 38.

m.p.: 126-128° C.

Recrystallizing solvent: ethanol.

Example 68

6-(4-Biphenylyl)-2-(2-aminoethyl)tetralin hydrochloride



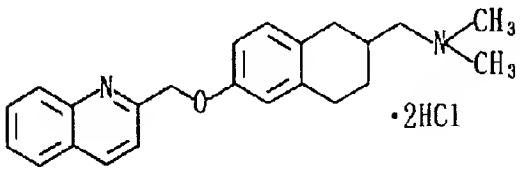
To a solution of 6-(4-biphenylyl)methoxy-2-(2-iodoethyl)tetralin (0.4 g) in DMF (10 ml) was added potasium phthalimide (0.4 g) and stirring was continued at room temperature for 2 days. The reaction mixture was diluted with water and the precipitate was collected by filtration. The precipitate was dissolved in ethanol (40 ml) and hydrazine monohydrate (5 ml) was added to the solution. After stirring at 50° C for 3 hr, the reaction mixture was concentrated. The residue was dissolved in ethyl acetate, which was washed with water, dried, and concentrated. The residue was dissolved in ethanol (20 ml) and 4 N hydrochloric acid/ethyl acetate (2 ml) was added and the solvent was

removed by concentration. The residue was recrystallized from methanol-ethyl acetate to obtain the titled compound (0.37 g).

m.p.: 262-265° C.

Example 69

2-(N,N-Dimethylamino)methyl-6-(2-quinolyl)methoxytetralin dihydrochloride

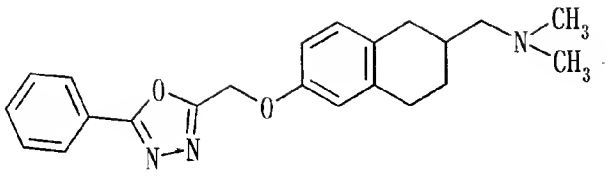


To a solution of 2-(N,N-dimethylamino)methyl-6-hydroxytetralin (153 mg, a free form of Reference Example 16) and 2-chloromethylquinoline hydrochloride (189 mg) in DMF (5 ml) was added potassium carbonate (260 mg) and the reaction mixture was stirred at room temperature for 26hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate: hexane =1 : 2) and then converted into its dihydrochloride, which was further recrystallized from methanol-ethyl acetate to obtain the titled compound (191 mg).

m.p.: 187-190° C (decomposed).

Example 70

2-(N,N-Dimethylamino)methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)methoxytetralin

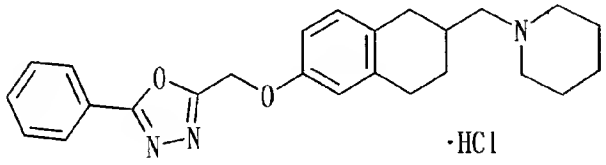


To a solution of 2-(N,N-dimethylamino)methyl-6-hydroxytetralin (206 mg, a free form of Reference Example 16) and 2-chloromethyl-5-phenyl-1,3,4-oxadiazole (231 mg) in DMF (5 ml) was added potassium carbonate (215 mg) and the reaction mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate: hexane =1 : 2) to obtain the titled compound (307 mg).

^{1}H NMR δ: 1.22-1.49(1H,m), 1.84-2.03(2H,m), 2.07-2.44(3H,m), 2.24(6H,s), 2.74-2.96(3H,m), 5.28(2H,s), 6.74-6.95(2H,m), 7.03(1H,d), 7.44-7.60(3H,m), 8.02-8.11(2H,m).

Example 71

6-(5-Phenyl-1,3,4-oxadiazol-2-yl)methoxy-2-piperidinomethyltetralin hydrochloride



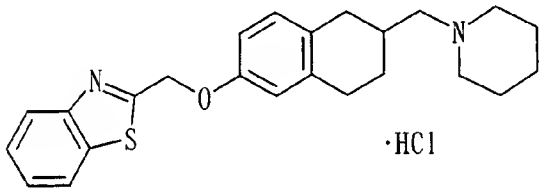
To a solution of 6-hydroxy-2-piperidinomethyltetralin (141 mg, free form of Reference Example 19) and 2-chloromethyl-5-phenyl-1,3,4-oxadiazole (148 mg) in DMF (3 ml) was added potassium carbonate (143 mg) and the reaction mixture

was stirred at room temperature for 24 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate: methanol =10 : 1) and alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4), and then converted into its hydrochloride, which was further recrystallized from methanol-diethyl ether to obtain the titled compound (175 mg).

m.p.: 217-219°C (decomposed).

Example 72

6-(2-Benzothiazolyl)methoxy-2-piperidinomethyltetralin hydrochloride



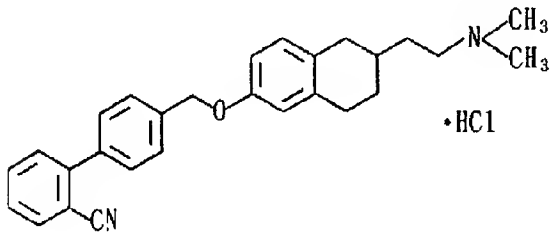
To a solution of 6-hydroxy-2-piperidinomethyltetralin hydrochloride (205 mg, Reference Example 19) and 2-chloromethylbenzothiazole (183 mg) in DMF (10 ml) was added potassium carbonate (327 mg) and the reaction mixture was stirred at room temperature for 4 days and further at 60°C for 7 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate : methanol =10 : 1), alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4) and converted into its hydrochloride, which was

recrystallized from methanol-ethyl acetate to obtain the titled compound (158 mg).

m.p.: 229-232°C.

Example 73

6-(2'-Cyanobiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin hydrochloride

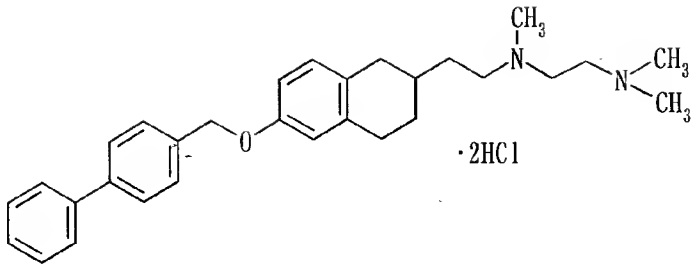


To a solution of 2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (72 mg, Reference Example 20) and 4-bromomethyl-2'-cyanobiphenyl (106 mg) in DMF (3 ml) was added sodium hydride (60% in oil, 36 mg) at 0°C and the reaction mixture was stirred at 0°C for 40 min. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4) and converted into its hydrochloride, which was further recrystallized from methanol-diisopropyl ether to obtain the titled compound (75 mg).

m.p.: 201-206°C.

Example 74

6-(4-Biphenylyl)methoxy-2-[[[N-[2-(N,N-dimethylamino)ethyl]-N-methyl]amino]ethyl]tetralin dihydrochloride

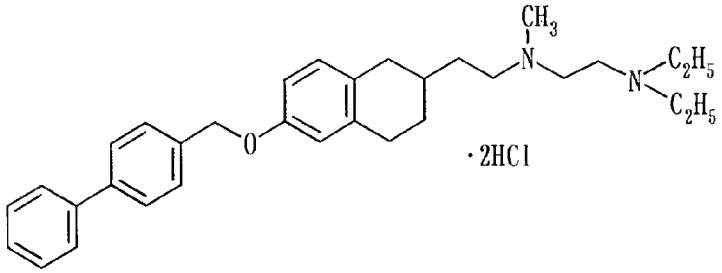


To a solution of [6-(4-biphenylyl)methoxy-2-tetralin]-N-[2-(N,N-dimethylamino)ethyl]-N-methylacetamide (495 mg) in THF (20 ml) was added lithium aluminum hydride (94 mg) at 0°C. The reaction mixture was stirred at room temperature for 50 min and heated under reflux for 2 hr. After cooling, the reaction mixture was poured into water and the precipitate was removed by filtration. The filtrate was concentrated and the residue was converted into its dihydrochloride, which was then recrystallized from methanol-ethyl acetate to obtain the titled compound (346 mg).

m.p.: 248-258°C (decomposed).

Example 75

6-(4-Biphenylyl)methoxy-2-[[[N-[2-(N,N-diethylamino)ethyl]-N-methyl]amino]ethyl]tetralin dihydrochloride



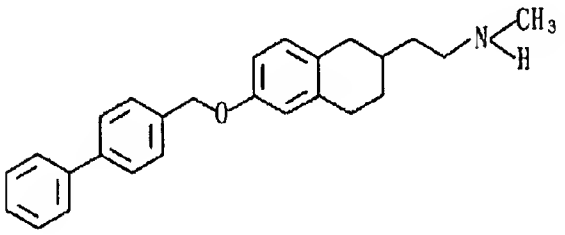
[6-(4-Biphenylyl)methoxy-2-tetralin]-N-[2-(N,N-diethylamino)ethyl]-N-methylacetamide hydrochloride

(320 mg) was converted into its free form and dissolved in THF (20 ml). Lithium aluminum hydride (68 mg) was added to the solution at 0°C. After stirring at room temperature for 4.5 hr, the reaction mixture was heated under reflux for 30 min. After cooling, the reaction mixture was diluted with water and the precipitate was removed by filtration. The filtrate was concentrated. The residue was converted into its dihydrochloride, which was washed with ethyl acetate and diisopropyl ether and settled out from methanol-diisopropyl ether to obtain the titled compound (281 mg) as an amorphous powder.

IR(KBr): 3314, 2926, 2635, 1611, 1505, 1267, 1235, 1163, 1011, 774 cm^{-1}.

Example 76

6-(4-Biphenylyl)methoxy-2-[2-(N-methylamino)ethyl]tetralin



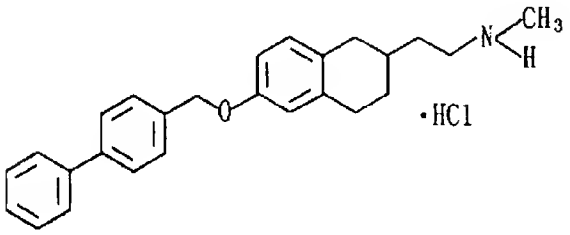
To a solution of [6-(4-biphenylyl)methoxy-2-tetralin]-N-methylacetamide (3.958 g) in THF (50 ml) was added 1M borane-THF complex (35 ml) at room temperature. The reaction mixture was heated under reflux for one hr. After cooling, the reaction mixture was diluted with water and 6 N aqueous hydrochloric acid (20 ml) at 0°C and stirred at room temperature for 3 hr. The reaction mixture was made basic by adding 1 N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and

concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 1) and then by recrystallization from ethyl acetate-hexane to obtain the titled compound (343 mg).

m.p.: 75-76°C.

Example 77

6-(4-Biphenylyl)methoxy-2-[2-(N-methylamino)ethyl]tetralin hydrochloride

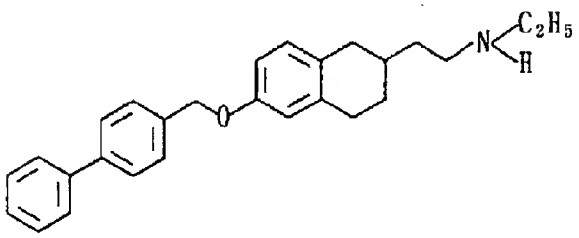


To a solution of [6-(4-biphenylyl)methoxy-2-tetralin]-N-methylacetamide (580 mg) in THF (15 ml) was added 1M borane-THF complex (5 ml) at room temperature. After stirring at room temperature for 2.5 hr, the reaction mixture was heated under reflux for 2.5 hr and cooled. The reaction mixture was diluted with water and 6 N aqueous hydrochloric acid (10 ml) at 0°C and stirred at room temperature for 8 hr. The reaction mixture was made basic by adding 1 N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 1) and then converted into its hydrochloride, which was washed with ethyl acetate to obtain the titled compound (167 mg).

m.p.: 233-237°C (decomposed).

Example 78

6-(4-Biphenylyl)methoxy-2-[2-(N-ethylamino)ethyl]tetralin

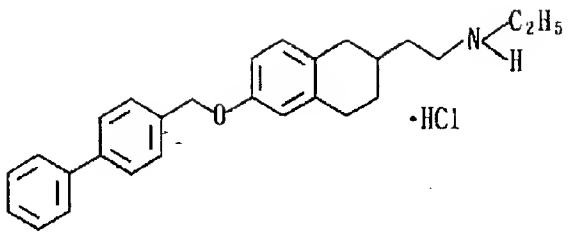


[6-(4-Biphenylyl)methoxy-2-tetralin]-N-ethylacetamide (4.009 g) was added to 1M borane-THF complex (20 ml) at room temperature. The reaction mixture was heated under reflux for 5 hr and cooled. Water and 6 N aqueous hydrochloric acid (10 ml) were added at 0°C and the reaction mixture was stirred at room temperature for 63 hr. The reaction mixture was made basic by adding 1 N aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The crude product was recrystallized from ethyl acetate-hexane to obtain the titled compound (2.851 g).

m.p.: 83-85°C.

Example 79

6-(4-Biphenylyl)methoxy-2-[2-(N-ethylamino)ethyl]tetralin hydrochloride

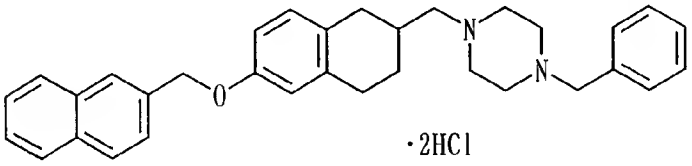


6-(4-Biphenylyl)methoxy-2-[2-(N-ethylamino)ethyl]tetralin (1.009 g) was converted into its hydrochloride. The hydrochloride was washed with methanol, ethyl acetate, and diethyl ether to obtain the titled compound (810 mg).

m.p.: 244-249°C (decomposed).

Example 80

2-(4-Benzylpiperazin-1-yl)methyl-6-(2-naphthyl)methoxytetralin dihydrochloride



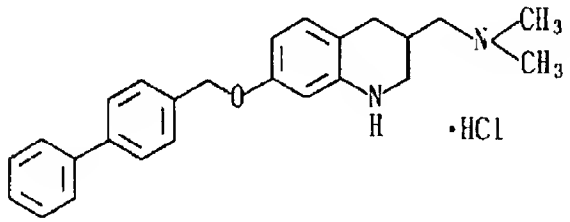
To a solution of 2-(4-benzylpiperazin-1-yl)methyl-6-hydroxytetralin (250 mg) in DMF (20 ml) was added sodium hydride (60% in oil, 30 mg) and the solution was stirred at room temperature for 30 min. A solution of 2-naphthylmethylbromide (162 mg) in DMF (10 ml) was added and the reaction mixture was stirred at room temperature for one hr, diluted with water, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate : hexane =1 : 1) and converted into its dihydrochloride,

which was then recrystallized from methanol-ethyl acetate to obtain the titled compound (240 mg).

m.p.: 210-212°C.

Example 81

7-(4-Biphenylyl)methoxy-3-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline hydrochloride

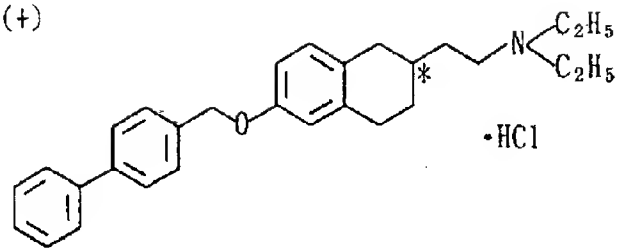


To a solution of 3-(dimethylamino)methyl-1,2,3,4-tetrahydro-7-quinolinol (344 mg), 4-biphenylylmethanol (368 mg), and triphenylphosphine (525 mg) in THF (20 ml) was added diethyl azodicarboxylate (348 mg). After stirring at room temperature for one hr, the reaction mixture was poured into 1 N aqueous hydrochloric acid and washed with ethyl acetate. The water layer was neutralized by 1 N aqueous sodium hydroxide, diluted with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate: hexane =1 : 4) and converted into its hydrochloride, which was further recrystallized from ethanol-diisopropyl ether to obtain the titled compound (214 mg).

m.p.: 183-184°C.

Example 82

(+)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin hydrochloride



To a solution of (+)-2-[2-(N,N-diethylamino)ethyl]-6-hydroxytetralin (4.5 g) in DMF (60 ml) was added sodium hydride (60 % in oil, 1.46 g) at 0° C. The reaction mixture was stirred at room temperature for 30 min and a solution of 4-chloromethylbiphenyl (4.08 g) in DMF (40 ml) was added. After stirring at room temperature for 2 hr, the reaction mixture was poured into water, neutralized with 1 N aqueous hydrochloric acid. Saturated aqueous sodium bicarbonate (50 ml) was added and the reaction mixture was extracted with combined solvent of ethyl acetate and THF (1 : 1). The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate to ethyl acetate : triethylamine =4 : 1) and converted into its hydrochloride, which was recrystallized from ethanol-diisopropyl ether to obtain the titled compound (6 g).

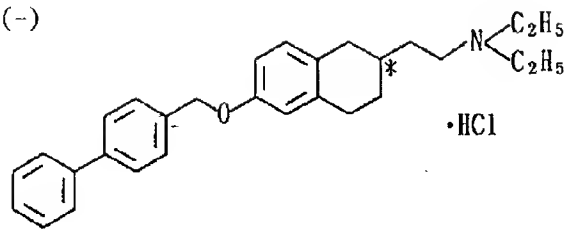
m.p.: 151-153° C.

$[\alpha]_D^{20}$=+42.1° (c=0.504 in methanol).

Optical purity: 97.6% e.e. (by HPLC analysis).

Example 83

(-)-6-(4-Biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin hydrochloride



The titled compound was synthesized by the similar manner as in Example 82.

Recrystallizing solvent; ethanol-diisopropyl ether

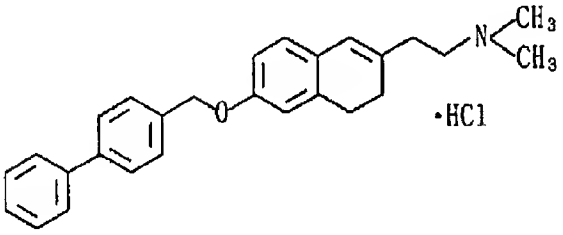
m.p.: 151-153°C.

$[\alpha]_D^{20}$=-40.6° (c=0.500 in methanol).

Optical purity: 98.9% e.e. (by HPLC analysis)

Example 84

6-(4-Biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]-3,4-dihydronaphthalene hydrochloride



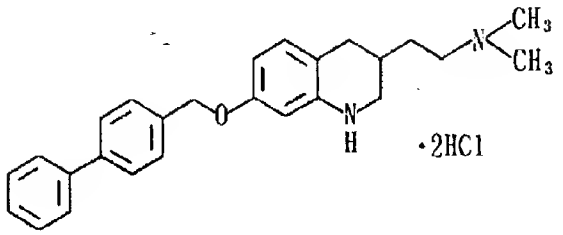
6-(4-Biphenylyl)methoxy-2-[2-(N-dimethylamino)ethyl]-3,4-dihydronaphthalene (44 mg) was converted into its hydrochloride, which was crystallized from methanol-diisopropyl ether to obtain the titled compound (43 mg).

m.p.: 233-243°C (decomposed).

Example 85

7-(4-Biphenylyl)methoxy-3-[2-(N,N-

dimethylamino)ethyl]-1,2,3,4-tetrahydroquinoline dihydrochloride

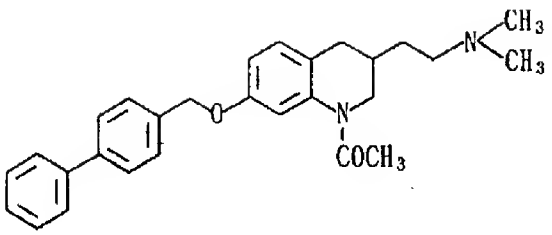


[7-(4-Biphenylyl)methoxy-1,2,3,4-tetrahydro-2-oxo-3-quinoline]-N,N-dimethylacetamide (1.407 g) was added to 1M borane-THF complex (15 ml) at room temperature. After stirring at room temperature for 15 hr and cooled. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was dissolved in THF (50 ml) and methanol (20 ml) and 1 N aqueous sodium hydroxide (20 ml) was added to the solution. The reaction mixture was heated under reflux for 5 days and cooled. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4) and converted into its dihydrochloride, which was recrystallized from ethanol to obtain the titled compound (647 mg).

m.p.: 185-192°C (decomposed).

Example 86

1-Acetyl-7-(4-biphenylyl)methoxy-3-[2-(N,N-dimethylamino)ethyl]-1,2,3,4-tetrahydroquinoline

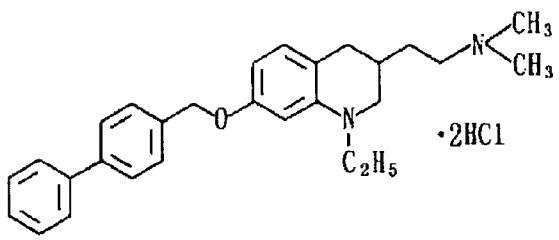


To a solution of 7-(4-biphenylyl)methoxy-3-[2-(N,N-dimethylamino)ethyl]-1,2,3,4-tetrahydroquinoline (250 mg) in THF (17 ml) was added triethylamine (0.33 ml) followed by addition of acetyl chloride (0.09 ml) at 0°C. After stirring in an ice bath for one hr, the reaction mixture was further stirred at room temperature for one hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 20 to 1 : 6) and the resulting precipitated crystals were washed with diisopropyl ether to obtain the titled compound (210 mg).

m.p.: 62.0-63.5°C

Example 87

7-(4-Biphenylyl)methoxy-3-[2-(N,N-dimethylamino)ethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline dihydrochloride

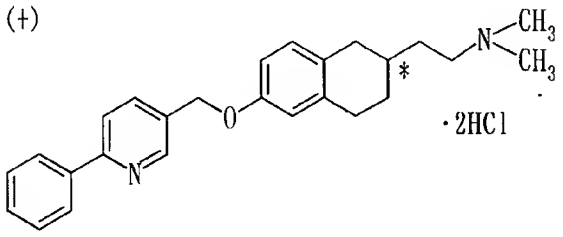


To a solution of 1-acetyl-7-(4-biphenylyl)methoxy-3-[2-(N,N-dimethylamino)ethyl]-1,2,3,4-tetrahydroquinoline (120 mg) in THF (1.5 ml) was added 1M borane-THF complex (0.9 ml) in an ice bath. After stirring at room temperature for 15 min, The reaction mixture was heated under reflux for 15 min and cooled. A small portion of water was added, followed by addition of 12 N aqueous sodium hydroxide (1.5 ml) and the reaction mixture was heated under reflux for 16 hr and cooled. The reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 20 to 1 : 7) and converted into its dihydrochloride, which was recrystallized from methanol-diisopropyl ether to obtain the titled compound (101 mg).

m.p.: 173-175°C (decomposed).

Example 88

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-(6-phenyl-3-pyridyl)methoxytetralin dihydrochloride



To a solution of (+)-2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (0.221 g) in DMF (5 ml) was added sodium hydride (60% in oil, 0.053 g) at room temperature. After stirring at 50°C for one hr, the reaction mixture was cooled to 0°C and a solution

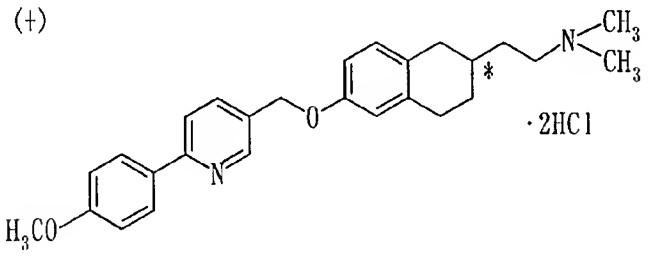
of 6-phenyl-3-pyridylmethyl bromide (76%, 0.366 g) in THF (5 ml) was added. The reaction mixture was stirred at 0°C for one hr, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate: hexane =1 : 4) and converted into its dihydrochloride, which was recrystallized from ethanol-ethyl acetate to obtain the titled compound (265 mg).

m.p.: 218-220°C.

$[\alpha]_D^{20}$=+43.5° (c=0.504 in methanol).

Example 89

(+)-2-[2-(N,N-Dimethylamino)ethyl]-6-[6-(methoxyphenyl)-3-pyridyl]methoxytetralin dihydrochloride



A mixture of (+)-6-(2-bromopyridin-5-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin dihydrochloride (0.2 g), toluene (8 ml), ethanol (1 ml), 2M aqueous sodium carbonate (1 ml) was stirred at room temperature for 10 min. 4-methoxyphenylboric acid (89 mg), and tetrakis(triphenylphosphine)palladium (27 mg) was added and the reaction mixture was heated under reflux under argon for 15 hr and cooled. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and saturated

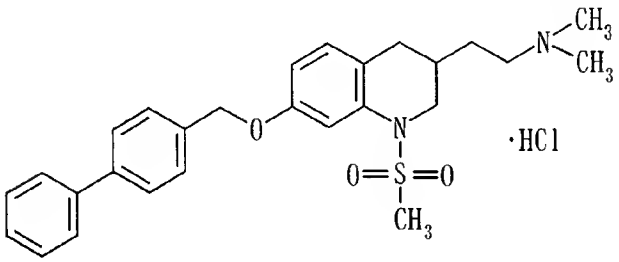
aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4) and then converted into its dihydrochloride, which was recrystallized from ethanol-ethyl acetate to obtain the titled compound (176 mg).

m.p.: 223-231°C (decomposed).

$[\alpha]_D^{20}$=+41.1° (c=0.494 in methanol).

Example 90

7-(4-Biphenylyl)methoxy-3-[2-(N,N-dimethylamino)ethyl]-1,2,3,4-tetrahydro-1-methylsulfonylquinoline hydrochloride



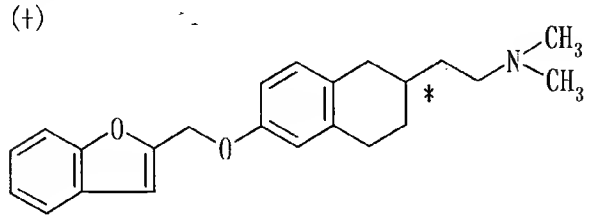
To a solution of 7-(4-biphenylyl)methoxy-3-[2-(N,N-dimethylamino)ethyl]-1,2,3,4-tetrahydroquinoline (110 mg) in pyridine (5 ml) was added methanesulfonyl chloride (0.03 ml) in an ice bath. The reaction mixture was stirred at room temperature for 3 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 2) and converted into its hydrochloride, which was then recrystallized from ethanol-ethyl acetate to obtain the titled compound (88 mg).

m.p.: 236-240°C (decomposed).

Example 91

(+)-6-(2-Benzofuranyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin

(+)



To a solution of (+)-2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (0.217 g) in DMF (5 ml) was added sodium hydride (60% in oil, 0.052 g) at room temperature. The reaction mixture was stirred at 50°C for one hr and cooled to 0°C. A solution of 2-chloromethylbenzofuran (0.187 g) in THF (5 ml) was added to the solution. The reaction mixture was stirred at 0°C for one hr, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride, dried, and concentrated. The residue was purified by alumina column chromatography (eluent: ethyl acetate : hexane =1 : 4) and recrystallized from ethyl acetate-hexane to obtain the titled compound (17 mg).

m.p.: 75-77°C.

$[\alpha]_D^{20}$=+56.8° (c=0.523 in methanol).

Formulation Example 1

(1)	Compound of Example 12	50 mg
(2)	Lactose	34 mg
(3)	Corn Starch	10.6 mg
(4)	Corn Starch (pasty)	5 mg
(5)	Magnesium Stearate	0.4 mg
(6)	Carboxymethyl Cellulose Calcium	20 mg
	Total	120 mg

These components (1) to (6) were mixed in an

ordinary manner, and tabletted, using a tabletting machine, to obtain tablets.

Experimental Example 1

Compounds of the present invention were tested for effect of inhibiting amyloid-β protein production in human neuroblastoma IMR-32 cells. Herein referred to were references, Science, 264, 1336 (1994) and Biochemistry, 34, 10272 (1995), etc.

(Methods)

a) Materials Used

Human neuroblastoma IMR-32 cells: purchased from American Type Culture Center

Dulbecco's modified Eagle's medium (hereinafter referred to as DMEM): purchased from Nippon Pharmaceutical Co.

Fetal calf serum (hereinafter referred to as FCS), and a mixture of penicillin (5000 U/ml)/streptomycin (5 mg/ml): both purchased from Bio Whittaker Co.

Phosphate buffered saline (hereinafter referred to as PBS): purchased from Flow Laboratories Co.

Block Ace (trade name): purchased from Dai-Nippon Pharmaceutical Co.

Bovine serum albumin (hereinafter referred to as BSA): purchased from Sigma Co.

Cultivation flask: manufactured by Falcon Co.

48-well Plate: manufactured by Coaster Co.

Standard $A\beta_{1-40}$ and $A\beta_{1-42}$: purchased from Bachem Co.

The other reagents used were commercially-available ones of special grade.

b) Test Method

(1) Cultivation of IMR-32 Cells

IMR-32 cells were cultivated in a flask (Falcon, 750 ml) containing 10% FCS/DMEM medium, in an atmosphere of 10% CO_2/90% air, at 37°C to be in

confluence. The cultivated cells were seeded into a 48-well plate in a density of 2.5 x 10^5 cells/well, and incubated therein for 3 days under the same condition as above. Then, the culture medium was removed through suction.

A dimethylformamide (DMF) solution containing a test compound was dissolved in 0.5 ml of 0.5% BSA/DMEM, and added to the plate, and the cells were incubated for further 24 hours. As the control, the same volume of DMF but not containing the test compound was dissolved in 0.5 ml of 0.5% BSA/DMEM, and added to the plate.

The supernatant was collected from the plate, and stored at -20°C or lower until the measurement of its Aβ content.

(2) Enzyme Immunoassay (EIA) for Aβ

BAN-50 antibody or BNT-77 antibody was used as the primary antibody. To determine the $A\beta_{1-40}$ of each sample, used was BA-27 antibody as the secondary antibody. To determine the $A\beta_{1-42}$ of each sample, used was BC-05 antibody as the secondary antibody.

BAN-50 antibody or BNT-77 antibody as dissolved in 0.1 M carbonic acid buffer (pH 9.6) in a concentration of 15 μg/ml was added to a polyethylene microtiter plate in an amount of 100 μl/well, and kept at 4°C overnight. The surface of the plate was washed three times with PBS, and 200 μl of a blocking solution (25% Block Ace/0.1% sodium azide/PBS) was added to the plate. Under this condition, the plate was kept at 4°C before the addition thereto of the supernatant prepared in (1).

Just before the addition of the supernatant, the surface of the plate was washed three times with PBS, and 50 μl of a buffer for primary reaction (20 mM phosphate buffer, pH 7.0; 400 mM NaCl; 2 mM EDTA; 10% Block Ace; 0.2% BSA; 0.05% sodium azide) was added to

the plate. Next, 100 µl of the supernatant and 100 µl of standard $A\beta_{1-40}$ or $A\beta_{1-42}$ as diluted in the buffer for primary reaction (to have a varying concentration of 1000, 200, 40 or 8 pg/ml) were added to the plate, and then kept overnight at 4° C.

The plate was washed three times with PBS, and 100 µl of an HRP-labeled secondary antibody (BA-27 antibody or BC-05 antibody labeled with HRP, horseradish peroxidase) as dissolved in a buffer for secondary reaction (20 mM phosphate buffer, pH 7.0; 400 mM NaCl; 2 mM EDTA; 1 % BSA) was added thereto. After having been left at room temperature for 6 hours, the plate was washed seven times with PBS, and 100 µl of a coloring reagent (TMB Peroxidase Substrate, trade name, manufactured by Kirkegaard & Perry Lab.) was added thereto. This was left at room temperature for 8 to 10 minutes, and 100 µl of 1 M phosphoric acid solution was added to the plate to stop the reaction. Then, using a plate reader (MTP-32 Microplate Reader, by Corona Co.), the sample on the plate was subjected to colorimetric determination (at 450 nm).

(Results)

Four wells were used for one dose of the test compound.

The effect of the test compound (10 µM) to inhibit the production and/or secretion of $A\beta_{1-40}$ and $A\beta_{1-42}$ was obtained in terms of the percentage (%) relative to the control. The data obtained are shown in Table 1.

[Table 1]

Test Compound (Ex. No.)	Aβ1-40 (%)	Aβ1-42 (%)
Example 12	74	75

The above data verify that compound (I) of the present invention and compound (I') have the effect of inhibiting amyloid-β protein production and/or secretion.

INDUSTRIAL APPLICABILITY

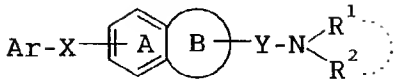
Compound (I) of the present invention has both an excellent inhibitory effect on amyloid-β protein production and/or secretion and an excellent stimulating effect on secreted form of amyloid precursor protein (sAPP) secretion, while having low toxicity, and has excellent mobility into the brain.

Compound (I') also has the inhibitory effect on amyloid-β protein production and/or secretion and stimulating effect on sAPP secretion.

Therefor, compounds (I) and (I') are useful as safe medicines for preventing and/or treating neurodegenerative disorders (e.g., Alzheimer's disease, Down's syndrome, senile dementia, Parkinson's disease, Creutzfeldt-Jacob disease, amyotrophic sclerosis on lateral fasciculus of spinal, diabetic neuropathy, Huntington's disease, multiple sclerosis, etc.), amyloid angiopathy, neurological disorders caused by cerebrovascular disorders (e.g., cerebral infarction, encephalorrhagia, etc.), a head injury or an injury of spinal cord, as well as ameliorating derangements (for example, depression, anxiety, compulsive neurosis, sleep disorders, etc.) caused by neurodegenerative disorders or neurological disorders, especially for neurodegenerative disorders caused by amyloid-β protein (e.g., Alzheimer's disease, Down's syndrome, etc.).

CLAIMS

1. A compound of the formula:



wherein Ar represents an aromatic ring assembly group which may be substituted or a fused aromatic group which may be substituted;

X represents (i) a bond, (ii) -S-, -SO- or $-SO_2-$, (iii) a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl, (iv) -CO-O- or (v) a group of the formula: $-(CH_2)p-X^1-$, $-(CH_2)p-X^1-(CH_2)q-$, $-(CH_2)r-CO-X^1-$, $-SO_2-NR^8-$ or $-(CH_2)r-SO_2-NR^8-$ wherein X^1 represents O or NR^8,

R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl, p represents an integer of 0 to 5, q represents an integer of 1 to 5, p+q is an integer of 1 to 5, and r represents an integer of 1 to 4;

Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted;

R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;

Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B represents a 4- to 8-membered ring which may be

further substituted apart from the group of the formula: -Y-NR^1R^2 wherein each symbol is as defined above;

provided that, when the fused ring to be formed by Ring A and Ring B is an indole ring, the group of the formula: -X-Ar wherein each symbol is as defined above is substituted on 4-, 6- or 7-position of the indole ring,

or a salt thereof.

2. A compound of claim 1, wherein

Ar is (i) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which rings are directly bonded to each other via a single bond, and which assembly group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-

carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or

(ii) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy;

R^8 is (a) a hydrogen atom,
(b) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl being optionally condensed with one benzene ring, C_{6-14} aryl or C_{7-19} aralkyl group which may be substituted by 1 to 5 substituents selected form the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy,

nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6}

alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, and (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-

membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or

(c) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl;

Y is a C_{1-6} alkylene, a C_{2-6} alkenylene, a C_{2-6} alkynylene or a group of the formula: $-(CH_2)m-Y^1-(CH_2)n-$ wherein $-Y^1-$ is -O-, -S-, -SO- or $-SO_2-$,

m is an integer of 0 to 4,

n is an integer of 1 to 5, and

m+n is an integer of 1 to 5;

R^1 and R^2 each is a hydrogen atom or a C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy,

carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy, C_{6-10} aryloxy and C_{6-10} aryl or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a 3- to 8-membered nitrogen-containing heterocyclic ring having one nitrogen atom and optionally having 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which ring may be substituted by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10}

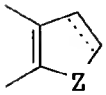
aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10}

aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of

nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (21) an oxo and (22) C_{7-19} aralkyl;

Ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, hydroxy and amino, apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B is a 4- to 8-membered ring of the formula:



wherein ---- is a single bond or a double bond, and Z is (i) a bond, (ii) a C_{1-4} alkylene, (iii) a C_{2-4} alkenylene, (iv) $-O-CH_2-$, (v) $-O-CH_2-CH_2-$ or (vi) a group of the formula: $-NR^{8a}-CH_2-$ or $-NR^{8a}-CH_2-CH_2-$ wherein R^{8a} is (a) a hydrogen atom, (b) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl being optionally condensed with one benzene ring, C_{6-14} aryl or C_{7-19} aralkyl group which may be substituted by 1 to 5 substituents selected form the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-

membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5

substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, and (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7- membered saturated cyclic

amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or

(c) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, which ring may be further substituted by 1 to 3 substituents selected from the group consisting of oxo, C_{1-6} alkyl and hydroxy, apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above.

3. A compound of claim 1, wherein Ar is an aromatic ring assembly group which may be substituted.

4. A compound of claim 3, wherein the aromatic rings of the aromatic ring assembly group are two or three aromatic rings selected from the group consisting of benzene, thiophene, pyridine, pyrimidine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, naphthalene and

benzofuran.

5. A compound of claim 3, wherein the aromatic ring assembly group is 2-, 3- or 4-biphenylyl.

6. A compound of claim 1, wherein Ar is a 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy.

7. A compound of claim 1, wherein X is a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom.

8. A compound of claim 1, wherein X is a C_{1-6} alkylene.

9. A compound of claim 1, wherein X is a group of the formula: $-(CH_2)p-X^1-$ wherein each symbol has the same

meaning as in claim 1.

10. A compound of claim 9, wherein p is 1.

11. A compound of claim 10, wherein X^1 is O.

12. A compound of claim 10, wherein X^1 is NR^{8b} wherein R^{8b} is hydrogen or C_{1-6} alkyl-carbonyl.

13. A compound of claim 1, wherein X^1 is a group of the formula: $-SO_2-NR^8-$ wherein each symbol has the same meaning as in claim 1.

14. A compound of claim 13, wherein R^8 is hydrogen.

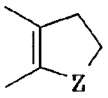
15. A compound of claim 1, wherein Y is a divalent C_{1-6} aliphatic hydrocarbon group.

16. A compound of claim 1, wherein Y is C_{1-6} alkylene.

17. A compound of claim 1, wherein R^1 and R^2 each is C_{1-6} alkyl.

18. A compound of claim 1, wherein Ring A is a benzene ring substituted by the group of the formula: -X-Ar wherein each symbol has the same meaning as in claim 1.

19. A compound of claim 1, wherein Ring B is a 4- to 8-membered ring of the formula:



wherein Z is (i) a bond, (ii) a C_{1-4} alkylene, (iii) a C_{2-4} alkenylene, (iv) $-O-CH_2-$, (v) $-O-CH_2-CH_2-$ or (vi) a group of the formula: $-NR^{8a}-CH_2-$ or $-NR^{8a}-CH_2-CH_2-$ wherein R^{8a} is (a) a hydrogen atom, (b) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl being optionally condensed with one benzene ring, C_{6-14} aryl or C_{7-19} aralkyl group which may be substituted by 1 to 5 substituents selected form the group consisting of (1) halogen atoms, (2) C_{1-3}

alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{3-6} cycloalkyl, (7) optionally halogenated C_{1-6} alkoxy, (8) optionally halogenated C_{1-6} alkylthio, (9) hydroxy, (10) amino, (11) mono-C_{1-6} alkylamino, (12) di-C_{1-6} alkylamino, (13) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl, (14) formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido or C_{1-6} alkylsulfonylamino, (15) C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy or nicotinoyloxy, (16) 5- to 7-membered saturated cyclic amino, (17) sulfo, (18) a phenyl or 5- or 6-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, each of which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6}

alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, (19) an aromatic ring assembly group which is composed of two or three rings selected from the class consisting of a C_{6-14} aromatic hydrocarbon, a C_{6-14} quinone and a 5- to 14-membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, are directly bonded to each other via a single bond, and which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-

membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, and (20) a fused bi- or tri-cyclic C_{10-14} aryl or 9- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, 5- to 7-membered saturated cyclic amino, formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl, C_{6-10} arylsulfonyl, formylamino, C_{1-6} alkyl-carboxamido, C_{6-10} aryl-carboxamido, C_{1-6} alkoxy-carboxamido, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-10} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, C_{6-10} aryl-

carbamoyloxy, nicotinoyloxy and C_{6-10} aryloxy, or

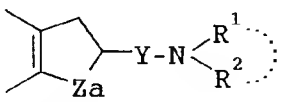
(c) formyl, carboxy, carbamoyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl,

which ring may be further substituted by 1 to 3 substituents selected from the group consisting of oxo, C_{1-6} alkyl and hydroxy, apart from the group of the formula: -Y-NR^1R^2 wherein each symbol has the same meaning as in claim 1.

20. A compound of claim 19, wherein R^{8a} is hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl.

21. A compound of claim 1, wherein Ring B is a 6-membered carbocyclic or heterocyclic ring substituted by a group of the formula: -Y-NR^1R^2 wherein each symbol has the same meaning as in claim 1.

22. A compound of claim 1, wherein Ring B is a ring of the formula:

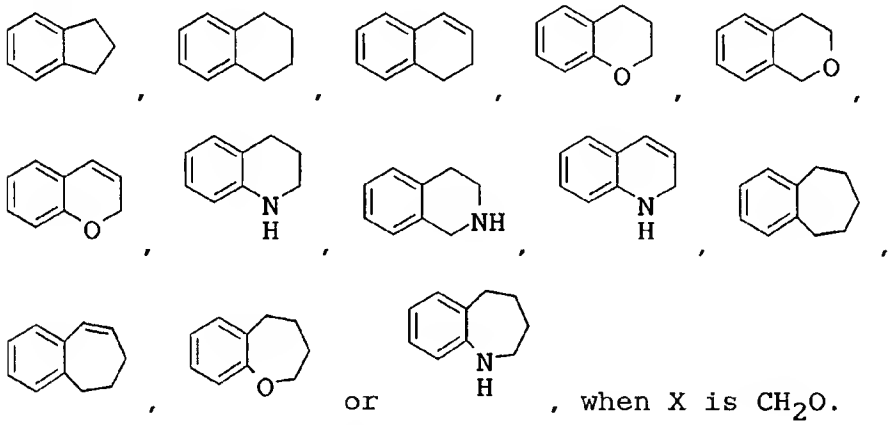


wherein Za is C_{1-3} alkylene or a group of the formula:

$-NR^{8c}-CH_2-$ wherein R^{8c} is hydrogen, optionally halogenated C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-10} aryl-carbonyl, C_{6-10} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{6-10} aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C_{1-6} alkylsulfonyl or C_{6-10} arylsulfonyl.

23. A compound of claim 22, wherein Za is ethylene.

24. A compound of claim 1, wherein the fused ring to be formed by Ring A and Ring B is a ring of the formula:



, when X is CH_2O.

25. A compound of claim 1, wherein

Ar is 2-, 3- or 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, formyl and C_{1-6} alkyl-carboxamido;

X is C_{1-3} alkylene which may contain an oxygen

atom;

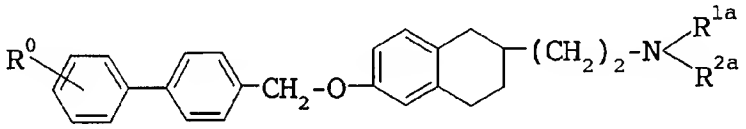
Y is C_{1-6} alkylene;

R^1 and R^2 each is C_{1-6} alkyl;

Ring A is a benzene ring substituted by the group of the formula: -X-Ar wherein each symbol has the same meaning as in claim 1; and

Ring B is a 6-membered carbocyclic or heterocyclic ring substituted by the group of the formula: $-Y-NR^1R^2$ wherein each symbol has the same meaning as in claim 1.

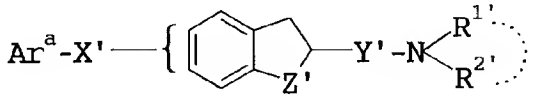
26. A compound of claim 1, which is a compound of the formula:



wherein R^0 is 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, formyl and C_{1-6} alkyl-carboxamido; and

R^{1a} and R^{2a} each is C_{1-6} alkyl, or a salt thereof.

27. A compound of claim 1, which is a compound of the formula:



wherein Ar^a is (i) 2, 3- or 4-biphenylyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, nitro, cyano, optionally halogenated C_{1-6} alkyl,

optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, amino, formyl and C_{1-6} alkyl-carboxamido, (ii) 4-(2-thienyl)phenyl or 4-(3-thienyl)phenyl, (iii) 4-(3-pyridyl)phenyl, (iv) 6-phenyl-3-pyridyl which may be substituted by a C_{1-6} alkoxy, (v) 5-phenyl-1,3,4-oxadiazol-2-yl, (vi) 4-(2-naphthyl)phenyl, (vii) 4-(2-benzofuranyl)phenyl, (viii) 1- or 2-naphthyl, (ix) 2-quinolyl, (x) 2-benzothiazolyl or (xi) 2-benzofuranyl;

X' is $-CH_2-O-$, $-SO_2-NH-$ or a group of the formula: $-CH_2-NR^{8'}-$ wherein $R^{8'}$ is hydrogen or C_{1-3} alkyl-carbonyl;

Y' is C_{1-6} alkylene;

Z' is $-CH_2-CH_2-$ or a group of the formula: $-NR^{8''}-CH_2-$ wherein $R^{8''}$ is hydrogen, C_{1-3} alkyl, C_{1-3} alkyl-carbonyl or C_{1-3} alkylsulfonyl; and

$R^{1'}$ and $R^{2'}$ each is C_{1-6} alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of di-C_{1-3} alkylamino, C_{1-3} alkoxy-carbonyl and phenyl, or

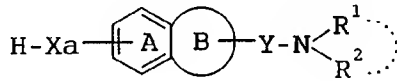
$R^{1'}$ and $R^{2'}$ form, taken together with the adjacent nitrogen atom, a pyrrolidin-1-yl, piperidino or piperazin-1-yl which may be substituted by 1 to 3 substituents selected from the group consisting of hydroxy, C_{1-3} alkoxy-carbonyl, piperidino, phenyl and benzyl, or a salt thereof.

28. A compound of claim 1 which is 6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
6-(4-biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin,
2-(N,N-dimethylamino)methyl-6-(4'-methoxybiphenyl-4-

yl)methoxytetralin,
(+)-6-(4-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-(4-biphenylyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin,
(+)-2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methylbiphenyl-4-yl)methoxytetralin,
(+)-2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methoxybiphenyl-4-yl)methoxytetralin,
(+)-6-(2',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin,
(+)-6-[4-(1,3-benzodioxol-5-yl)phenyl]methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, or
(+)-6-(3',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, or a salt thereof.

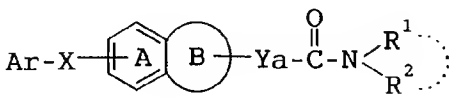
29. A process for producing of a compound of claim 1, which comprises;

i) subjecting a compound of the formula:



wherein Xa represents an oxygen atom, a sulfur atom which may be oxidized or a group of the formula: NR^8 wherein R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl; and the other symbols have the same meanings as in claim 1, or a salt thereof, to alkylation or acylation and optionally followed by aryl-coupling of the resultant compound;

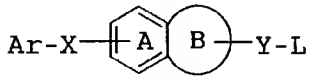
ii) subjecting a compound of the formula:



wherein Ya represents a group to be formed by removing a methylene from Y; and the other symbols have the same meanings as in claim 1, or a salt thereof, to

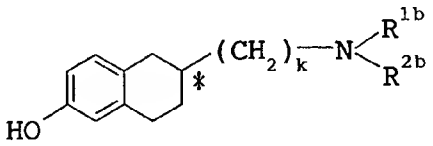
reduction; or

iii) subjecting a compound of the formula:



wherein L represents a leaving group; and the other symbols have the same meanings as in claim 1, to amination.

30. An optical isomer of the compound of the formula:



wherein R^{1b} and R^{2b} each represents methyl or ethyl, k represents 1 or 2, and * indicates the position of the asymmetric carbon, or a salt thereof.

31. A pharmaceutical composition which comprises a compound of claim 1.

32. A pharmaceutical composition of claim 31 which is an inhibitor for production and/or secretion of amyloid-β protein.

33. A pharmaceutical composition of claim 31 which is for preventing and/or treating neurodegenerative diseases caused by amyloid-β protein.

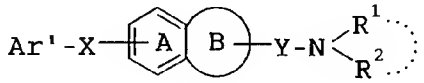
34. A pharmaceutical composition of claim 32, wherein the neurodegenerative disease caused by amyloid-β protein is Alzheimer's disease.

35. A method of inhibiting production and/or secretion of amyloid-β protein in mammal, which comprises administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent.

36. Use of a compound of claim 1 or a salt thereof for manufacturing a pharmaceutical composition for

inhibiting production and/or secretion of amyloid-β protein.

37. An inhibitor for production and/or secretion of amyloid-β protein, which comprises a compound of the formula:



wherein Ar' represents an aromatic group which may be substituted;

X represents (i) a bond, (ii) -S-, -SO- or $-SO_2-$, (iii) a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl, (iv) -CO-O- or (v) a group of the formula: $-(CH_2)p-X^1-$, $-(CH_2)p-X^1-(CH_2)q-$, $-(CH_2)r-CO-X^1-$, $-SO_2-NR^8-$ or $-(CH_2)r-SO_2-NR^8-$

wherein X^1 represents O or NR^8,

R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl, p represents an integer of 0 to 5, q represents an integer of 1 to 5, p+q is an integer of 1 to 5, and r represents an integer of 1 to 4;

Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted;

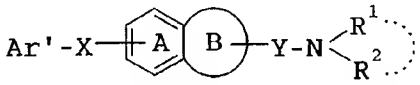
R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;

Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar

wherein each symbol is as defined above; and
Ring B represents a 4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above,
or a salt thereof.

38. A method of inhibiting production and/or secretion of amyloid-β protein in mammal, which comprises administering to said mammal an effective amount of a compound of the formula:



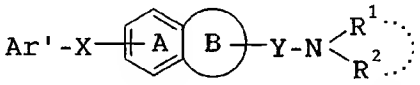
wherein Ar' represents an aromatic group which may be substituted;
X represents (i) a bond, (ii) -S-, -SO- or $-SO_2-$, (iii) a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl, (iv) -CO-O- or (v) a group of the formula: $-(CH_2)p-X^1-$, $-(CH_2)p-X^1-(CH_2)q-$, $-(CH_2)r-CO-X^1-$, $-SO_2-NR^8-$ or $-(CH_2)r-SO_2-NR^8-$
wherein X^1 represents O or NR^8,
R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl, p represents an integer of 0 to 5, q represents an integer of 1 to 5, p+q is an integer of 1 to 5, and r represents an integer of 1 to 4;
Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted;
R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;

Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B represents a 4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above, or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent.

39. Use of a compound of the formula:



wherein Ar' represents an aromatic group which may be substituted;

X represents (i) a bond, (ii) -S-, -SO- or $-SO_2-$, (iii) a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl, (iv) -CO-O- or (v) a group of the formula: $-(CH_2)p-X^1-$, $-(CH_2)p-X^1-(CH_2)q-$, $-(CH_2)r-CO-X^1-$, $-SO_2-NR^8-$ or $-(CH_2)r-SO_2-NR^8-$ wherein X^1 represents O or NR^8,

R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl, p represents an integer of 0 to 5, q represents an integer of 1 to 5, p+q is an integer of 1 to 5, and r represents an integer of 1 to 4;

Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom

and may be substituted;

R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or

R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;

Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and

Ring B represents a 4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above, or a salt thereof for manufacturing a pharmaceutical composition for inhibiting production and/or secretion of amyloid-β protein.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/JP 98/00780

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C217/74 A61K31/135 C07C255/54 C07D295/08 C07C233/43
C07D211/26 C07C311/21 C07C211/60 C07C323/19 C07D333/16
C07D213/30 C07D211/44 C07C217/76 C07C233/25 C07D317/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents ere included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 754 455 A (CONSEJO SUPERIOR INVESTIGACION ;UNIV BARCELONA AUTONOMA (ES)) 22 January 1997 cited in the application see claims	1-39
X	EP 0 332 064 A (THOMAE GMBH DR K) 13 September 1989 see claims	1,3,9, 11, 15-25,31
A	WO 95 32967 A (SMITHKLINE BEECHAM PLC ;HAM PETER (GB); GASTER LARAMIE MARY (GB);) 7 December 1995 cited in the application	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the ert which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document pubfished after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
4 June 1998	12.06.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaen 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pauwels, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/JP 98/00780

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/80 C07D211/60 C07C229/14 C07D215/14 C07D271/10
C07D277/64 C07D215/20 C07D215/00 C07D215/58 C07D213/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropnate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation ot box C.

☒ Patent family members are listed in annex.

° Special categories ot cited documents :

"A" document detining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specitied)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" documenl published prior to the international filing date but later than the priority date claimed

"T" later document published after the international tiling date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document ot particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion ot theinternational search	Date ot mailing of the international search report
4 June 1998	12. 06. 98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Pauwels, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 98/00780

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 35 and 38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

The scope of the claims is so broad that a complete search appears impossible. For determining the scope of the International Search due account has been taken of Rule 33.3. PCT; special emphasis was put on the subject-matter as illustrated by the examples.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter ional Application No
PCT/JP 98/00780

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0754455 A	22-01-1997	ES 2098186 A	16-04-1997
		CA 2187460 A	15-08-1996
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EP 0332064 A	13-09-1989	DE 3807813 A	21-09-1989
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